ANNEXON biosciences

PROTECTION OF VISION AND STRUCTURE IN GA

Saturday September 21, 2024

13:00-14:00

Room 113/114

EuRetina 2024

Annexon Symposium Agenda Sep 21st 13:00-14:00

Jeff Heier, MD

C1q driven neurodegeneration in GA and relationship to structure

Chair: Usha Chakravarthy, MD, PhD, CBE

ANX007: Visual acuity protection and safety in Phase 2 ARCHER trial

Paulo Eduardo Stanga, MD

Linking structure to function: protection of vision associated structures with ANX007

Chair: Usha Chakravarthy, MD, PhD, CBE

ANX007: What's Next?

?

Q&A Panel

Please Hold Your Questions, a Q&A panel will be held at the end of the Symposium

ANNEXON biosciences

Housekeeping

- If you have not done so, please scan your badges with our attendants so we can send you any follow-up materials
- Please hold your questions until all speakers have completed the symposium, we will be hosting a Q&A panel after the talks have concluded
- If you have any questions after the symposium, please approach the Annexon team members in the room, we will be around for a few minutes after the symposium concludes

ANNEXON biosciences

C1Q DRIVEN NEURODEGENERATION AND RELATIONSHIP TO STRUCTURE IN AMD

Jeff Heier, MD

Director, Retina Service

Director, Retina Research

Ophthalmic Consultants of Boston

Chief Scientific Officer

Ocular Therapeutix

Targeting C1q-Mediated Neurodegeneration – Preservation of Synapses & Neuronal Function

Dr. Ben Barres discovery of C1q's role in neurodegeneration (2007) › **Spawned entire fields and Validated in labs world-wide[1]** › **Anti-C1q protective in several disease models**

Ben Barres, M.D., Ph.D.
Discoverer of C1q Technology
Chair of Neurobiology at Stanford University
Scientific Co-Founder, Annexon

KEY DISCOVERIES:

1. C1q normally functions to eliminate excess synapses in development[1]
2. C1q-mediated synaptic pruning is common pathway of neurodegeneration
3. C1q inhibition protects against synapse loss and neurodegeneration in several disease models[2]

- Alzheimer's disease
- Amyotrophic Lateral Sclerosis
- Frontotemporal dementia
- Geographic Atrophy
- Glaucoma
- Guillain-Barré Syndrome
- Huntington's disease
- Retinal ischemia
- Schizophrenia
- Spinal muscular atrophy
- Traumatic brain injury

[1]Stevens, et al., 2007 DOI 10.1016/j.cell.2007.10.036; Schafer et al., 2012 DOI 10.1016/j.neuron.2012.03.026; Hong, et al., 2016 doi: 10.1126/science.aad8373; Lui et al., 2016 doi.org/10.1016/j.cell.2016.04.001; [2]Yednock, et al, 2022, doi.org/10.1186/s40942-022-00431-y

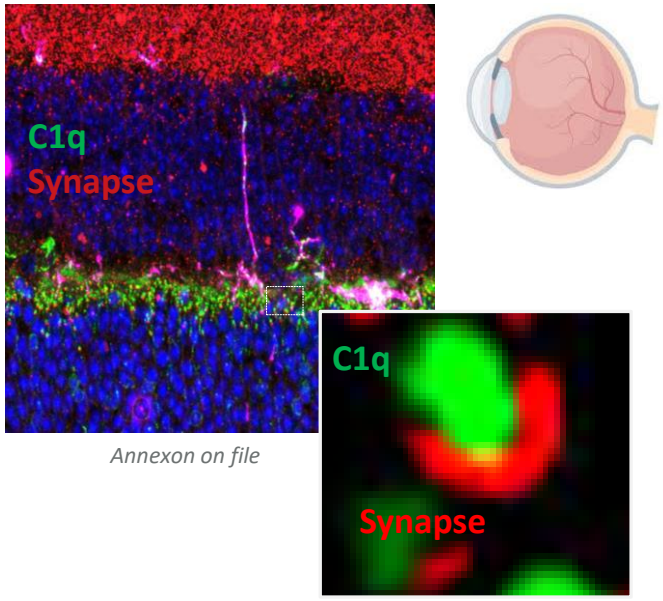
ANNEXON biosciences

C1q is Common Driver of Neurodegeneration in Both the Central (CNS) and Peripheral Nervous System (PNS)

C1q directly binds to synapses on stressed neurons, triggering elimination

C1q targeting synapses for elimination in the retina[1]

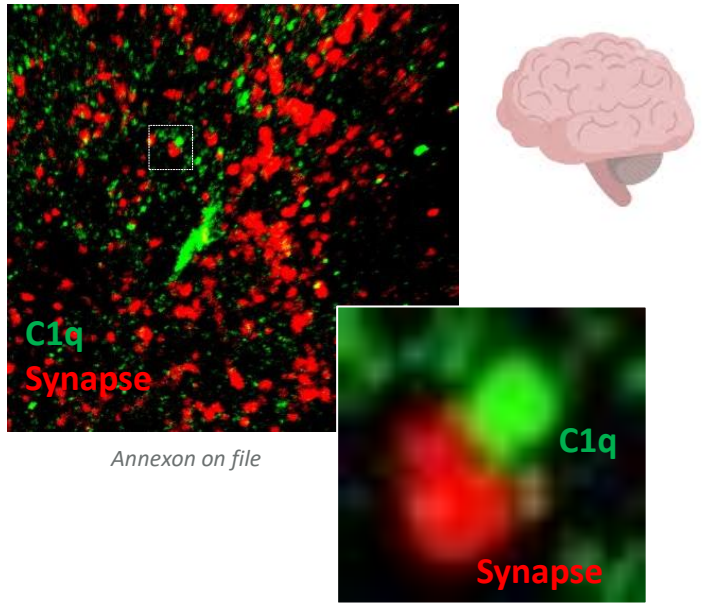
MODEL OF PHOTORECEPTOR DEGENERATION



Annexon on file

C1q targeting synapses for elimination in the brain[2]

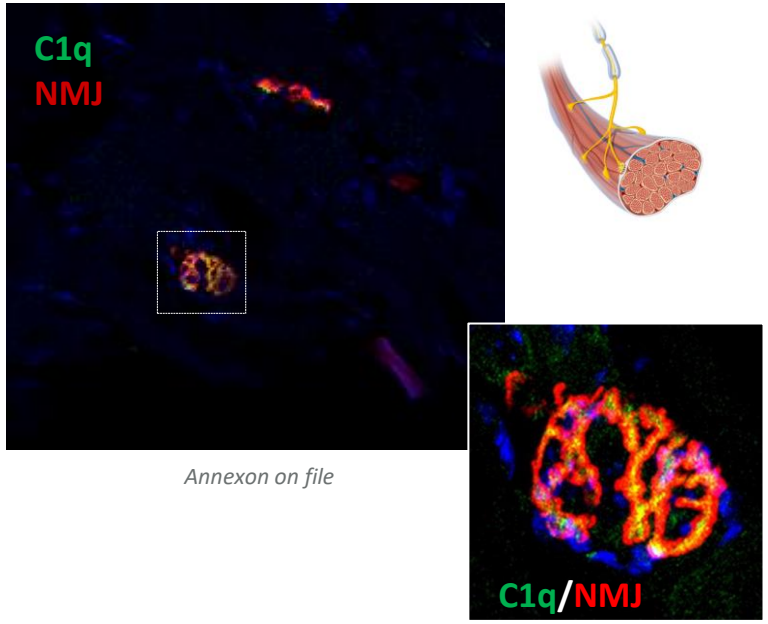
MODEL OF HUNTINGTON'S DISEASE



Annexon on file

C1q targeting neuromuscular junction (NMJ) for elimination in the PNS[3]

MODEL OF AMYOTROPHIC LATERAL SCLEROSIS



Annexon on file

C1Q INHIBITION PROTECTS AGAINST SYNAPSE LOSS AND NEURODEGENERATION IN SEVERAL DISEASE MODELS[4]

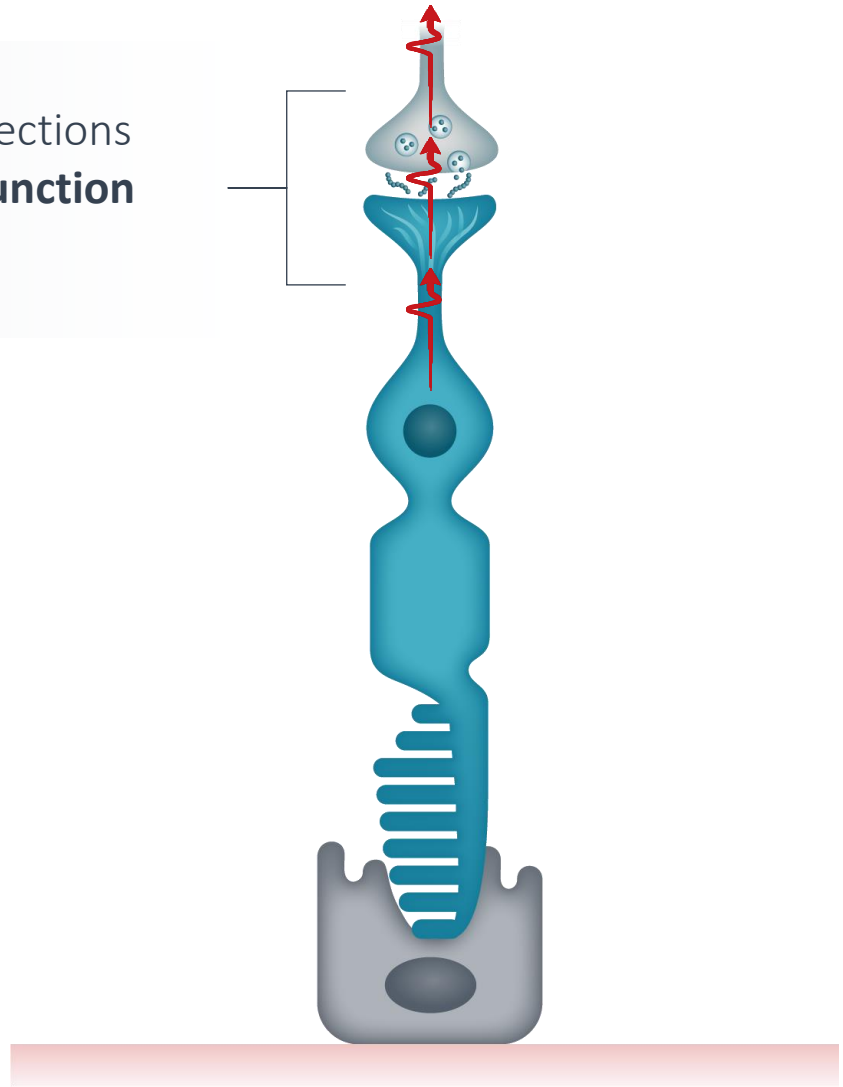
[1]Stevens, et al., 2007 DOI 10.1016/j.cell.2007.10.036; [2]Wilton, et al., 2023, doi: 10.1038/s41591-023-02566-3; [3]Idriss, et al., 2016 doi: 10.1186/s12974-016-0538-2
[4]Yednock, et al, 2022, doi.org/10.1186/s40942-022-00431-y

ANNEXON biosciences

Anti-C1q: A Distinct Neuroprotective Mechanism

C1q drives photoreceptor synapse & cell loss and neuroinflammation

Synapses are connections **vital to neuronal function and survival**



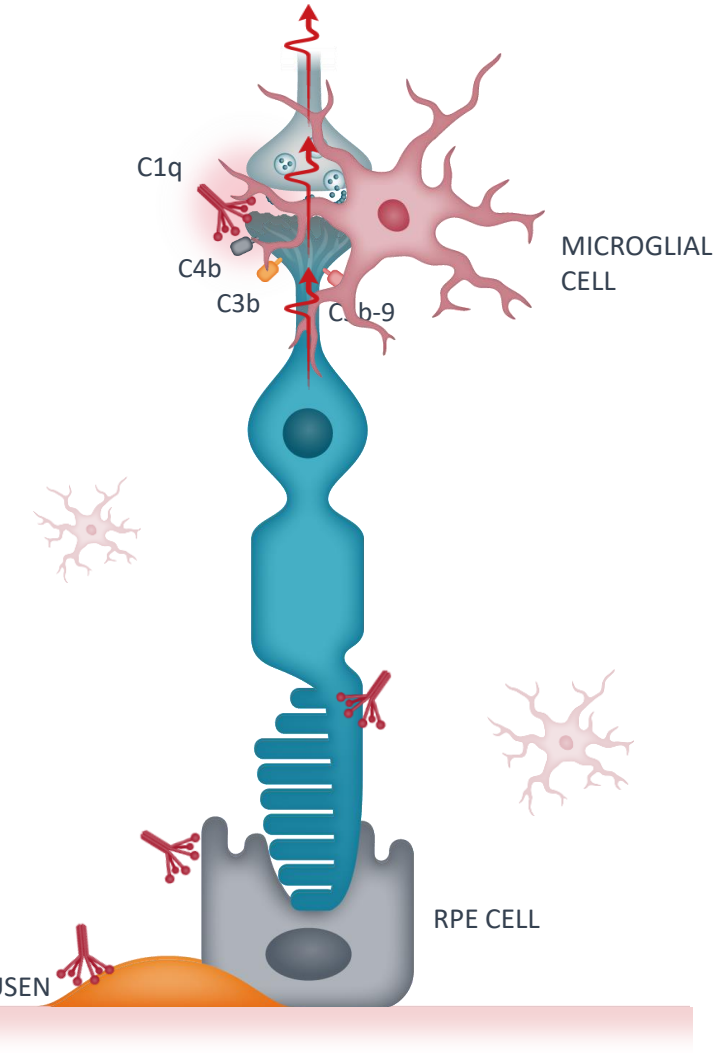
[1]Davies et al., 1987 J Neurological Sci 78:151; Terry, et al., 1991 Ann Neurol 30:572: [2]Tassoni, et al., SFN 2022; Annexon data on file; Jiao, et al., 2018 *Mol Neurodegener* **13**:45; Katschke, 2018 Sci Rep. **8**:7348. [3]Lansita, et al., 2017 *International Journal of Toxicology*, **36**:449; [4]Yednock, et al., 2022 *Int J Retina Vitreous* **8**:79

ANNEXON biosciences

Anti-C1q: A Distinct Neuroprotective Mechanism

C1q drives photoreceptor synapse & cell loss and neuroinflammation

C1q anchors classical pathway activation on stressed photoreceptor synapses and tags them for removal



In GA, C1q also binds photoreceptor cell outer segments, cellular breakdown products and drusen (e.g., CRP, amyloid)[4]

LOSS OF SYNAPSE = LOSS OF NEURONAL FUNCTION[1]

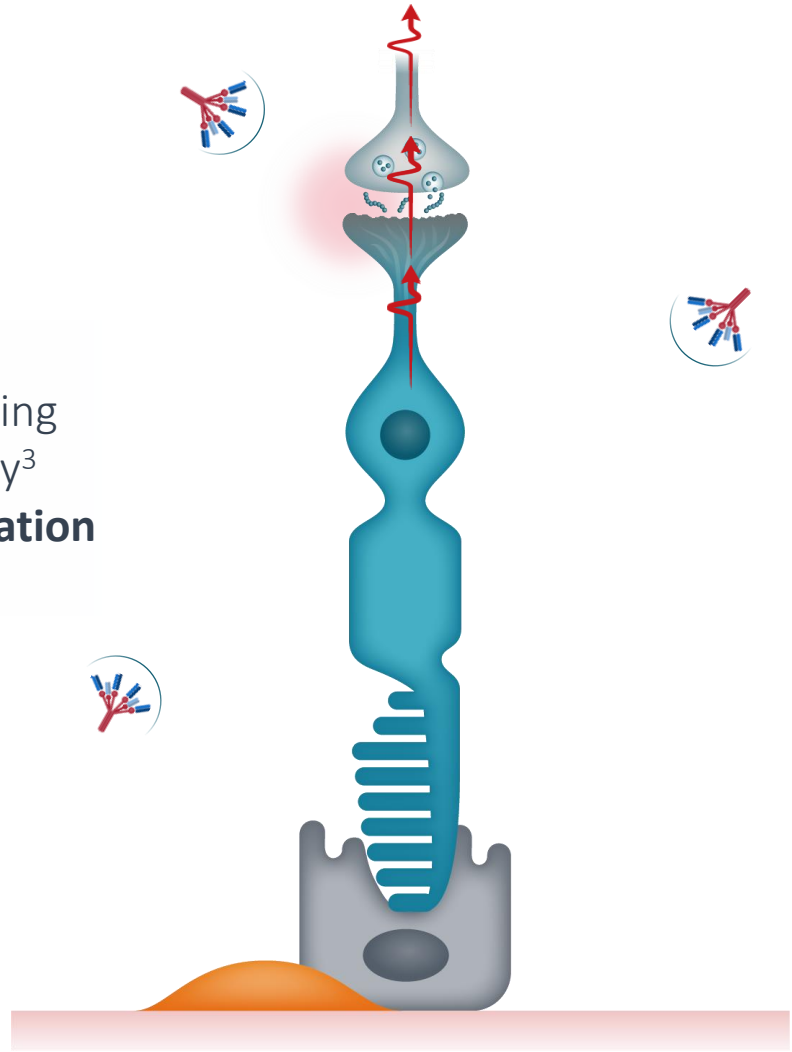
[1]Davies et al., 1987 J Neurological Sci 78:151; Terry, et al., 1991 Ann Neurol 30:572: [2]Tassoni, et al., SFN 2022; Annexon data on file; Jiao, et al., 2018 *Mol Neurodegener* **13**:45; Katschke, 2018 Sci Rep. **8**:7348. [3]Lansita, et al., 2017 *International Journal of Toxicology*, **36**:449; [4]Yednock, et al., 2022 *Int J Retina Vitreous* **8**:79

ANNEXON biosciences

Anti-C1q: A Distinct Neuroprotective Mechanism

C1q drives photoreceptor synapse & cell loss and neuroinflammation

ANX007 inhibits C1q and all damaging components of the classical pathway[3] and **protects synapses from elimination**

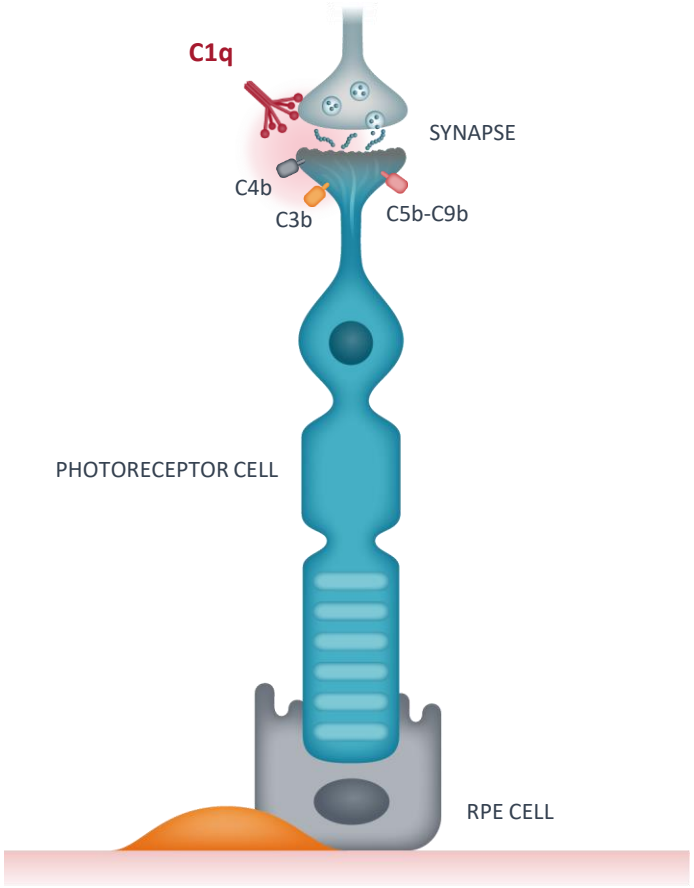


[1]Davies et al., 1987 J Neurological Sci 78:151; Terry, et al., 1991 Ann Neurol 30:572: [2]Tassoni, et al., SFN 2022; Annexon data on file; Jiao, et al., 2018 *Mol Neurodegener* **13**:45; Katschke, 2018 Sci Rep. **8**:7348. [3]Lansita, et al., 2017 *International Journal of Toxicology*, **36**:449; [4]Yednock, et al., 2022 *Int J Retina Vitreous* **8**:79

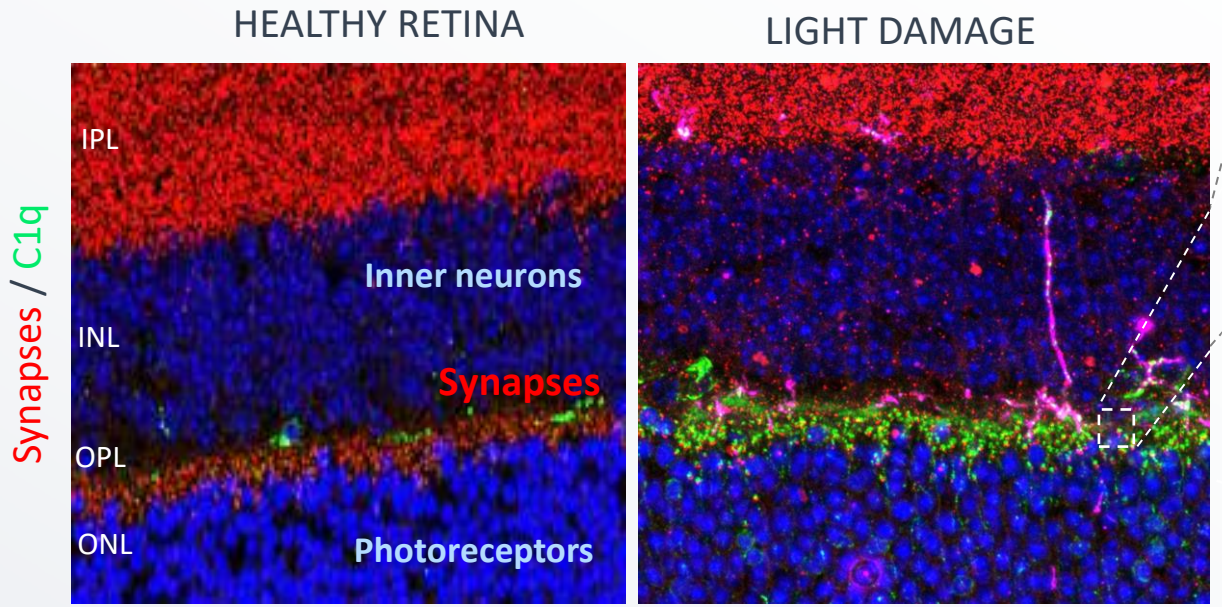
ANNEXON biosciences

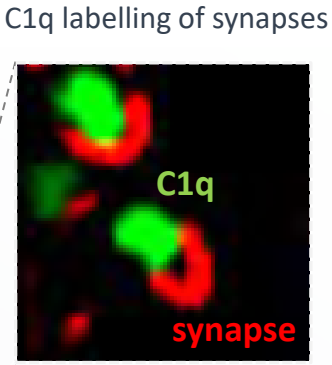
Rationale for C1q in GA: C1q Recognizes and Eliminates Photoreceptor Synapses in a Model of Photoreceptor Degeneration

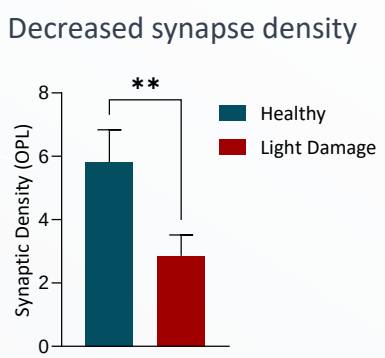
C1q binds stressed photoreceptor synapses



C1Q SELECTIVELY RECOGNIZES SYNAPSES ON DAMAGED PHOTORECEPTOR NEURONS IN A MODEL OF LIGHT-INDUCED DAMAGE





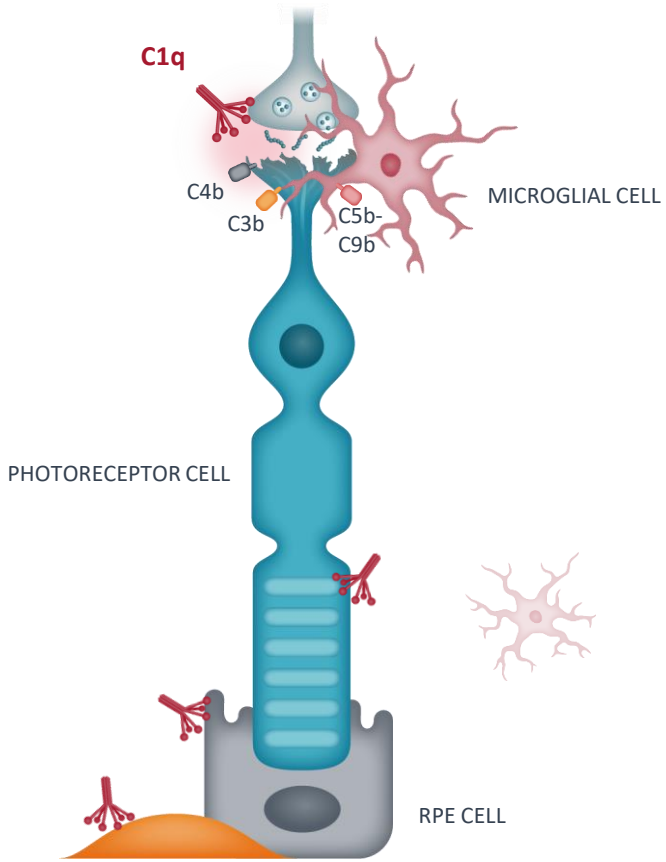


Tassoni, et al., ARVO, 2024 and Annexon on file

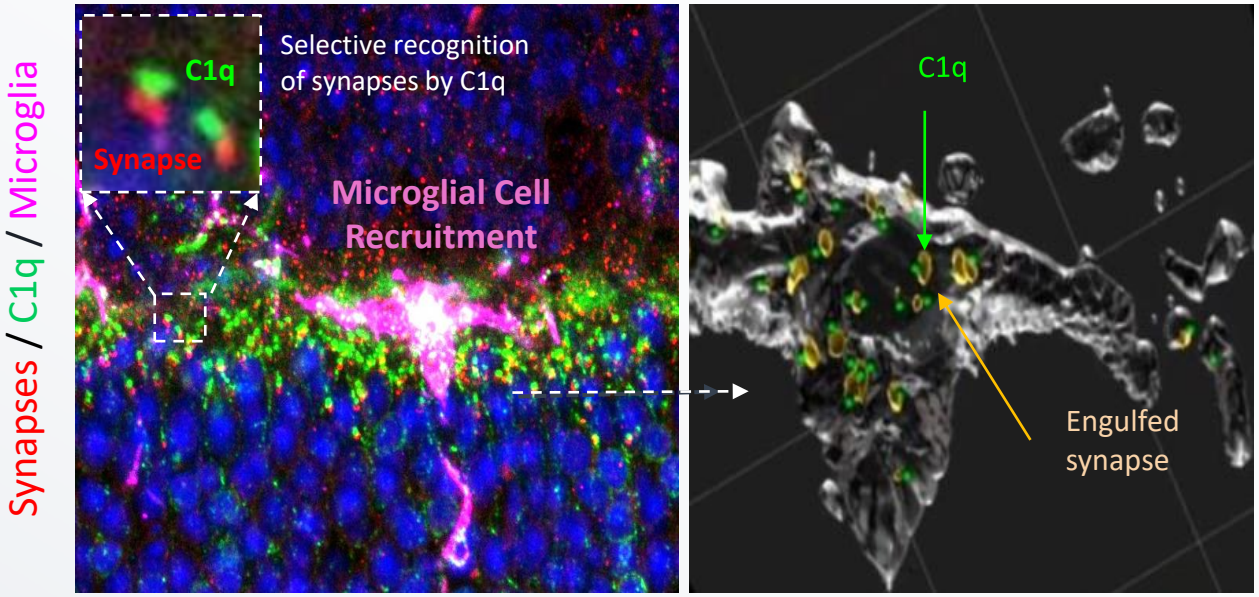
ANNEXON biosciences

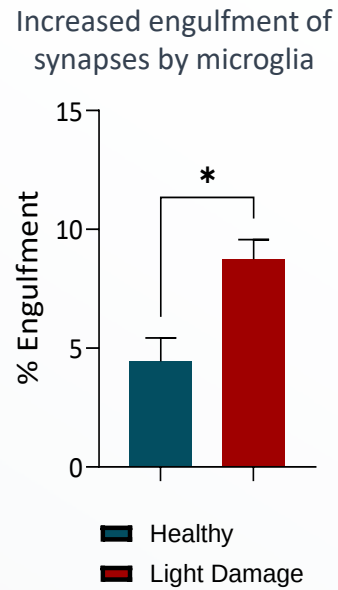
Rationale for C1q in GA: C1q Drives Synapse Destruction and Removal by Microglia in a Model of Photoreceptor Degeneration

C1q binds stressed photoreceptor synapses
and tags them for removal by microglia cells



MICROGLIAL ENGULFMENT OF C1Q-COATED SYNAPSES



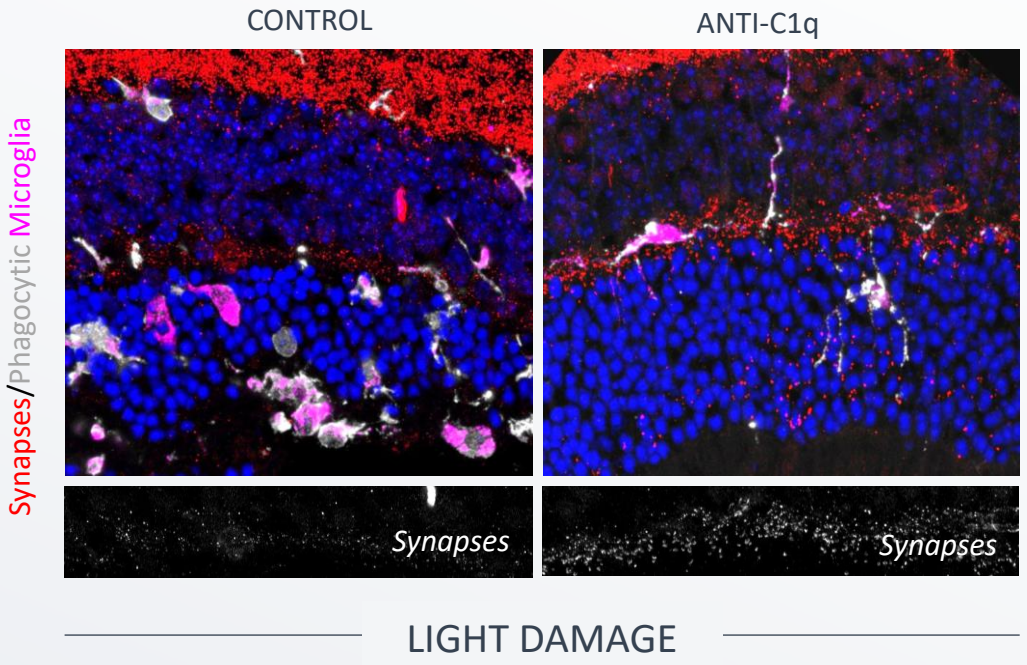


Tassoni, et al., ARVO, 2024 and Annexon on file

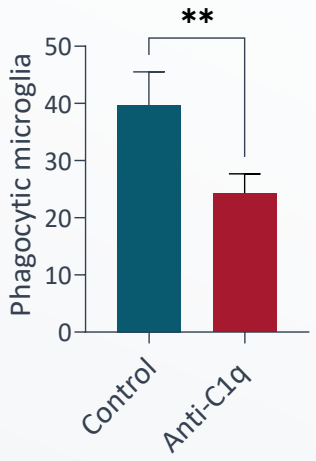
ANNEXON biosciences

Rationale for C1q in GA: Anti-C1q Protected Photoreceptor Cells and Function in Models of Photoreceptor Damage

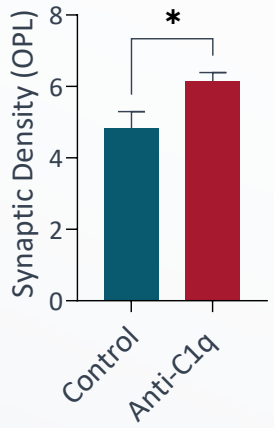
ANTI-C1Q TREATMENT REDUCED INFLAMMATION AND PRESERVED **PHOTORECEPTOR SYNAPSES AND CELL BODIES**



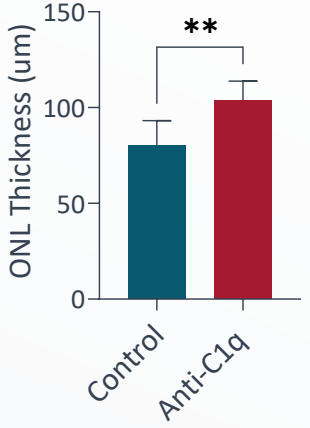
Reduced reactive **microglia**



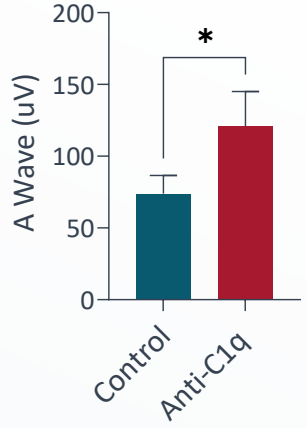
Protected photoreceptor **synapses**



Protected photoreceptor **cell bodies**



Protected retinal **function**

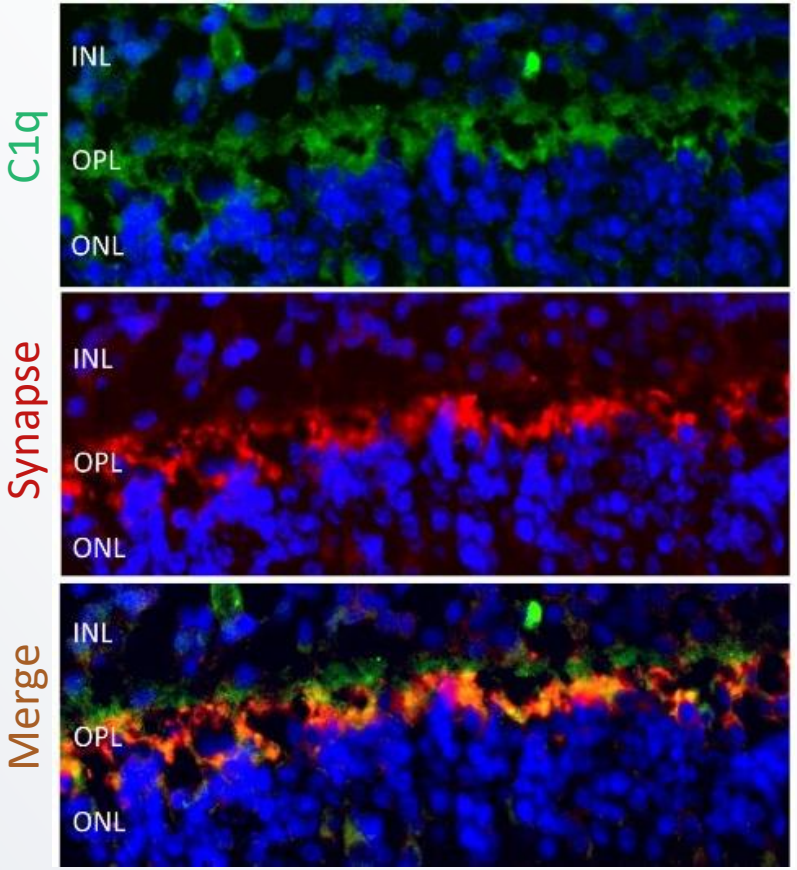


Tassoni, et al., ARVO 2024; Annexon data on file; Jiao, et al., 2018 *Mol Neurodegener* **13**:45;.

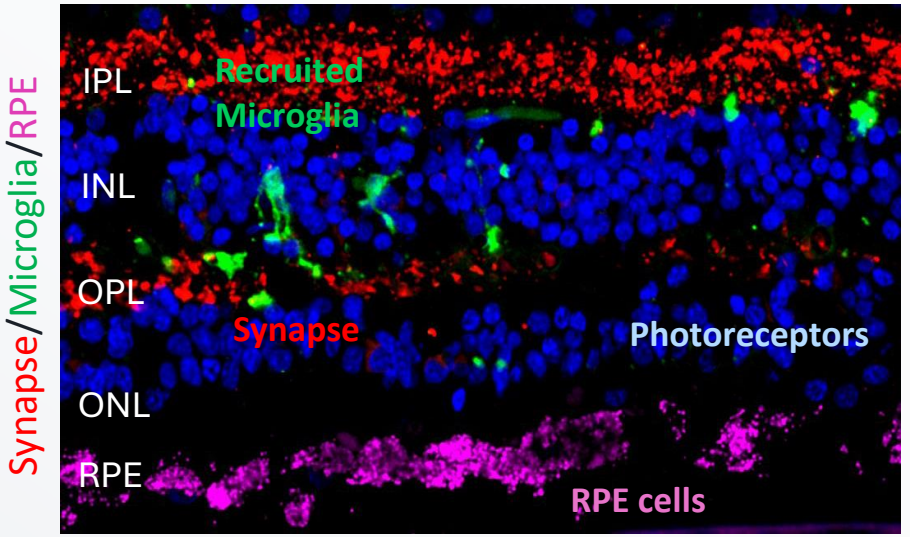
ANNEXON biosciences

Evidence of C1q in Human GA: C1q Deposition on Photoreceptor Synapses and Microglia Recruitment in Postmortem GA Retinal Tissue

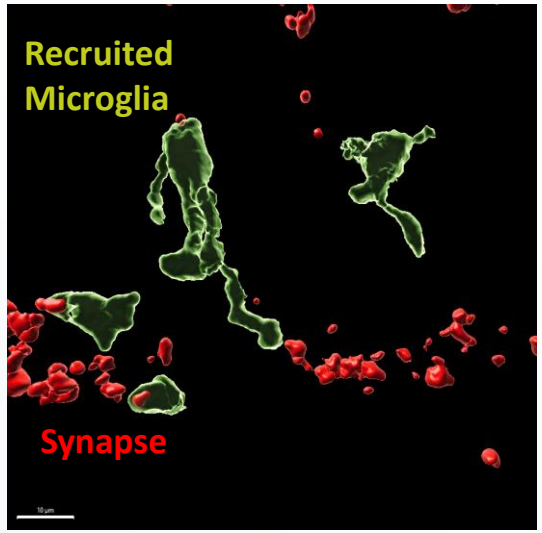
C1Q DEPOSITION ON PHOTORECEPTOR SYNAPSES



MICROGLIA RECRUITMENT AND **PHOTORECEPTOR SYNAPSE LOSS** IN POSTMORTEM GA RETINA TISSUE



Microglial Recruitment and Synapse Engulfment



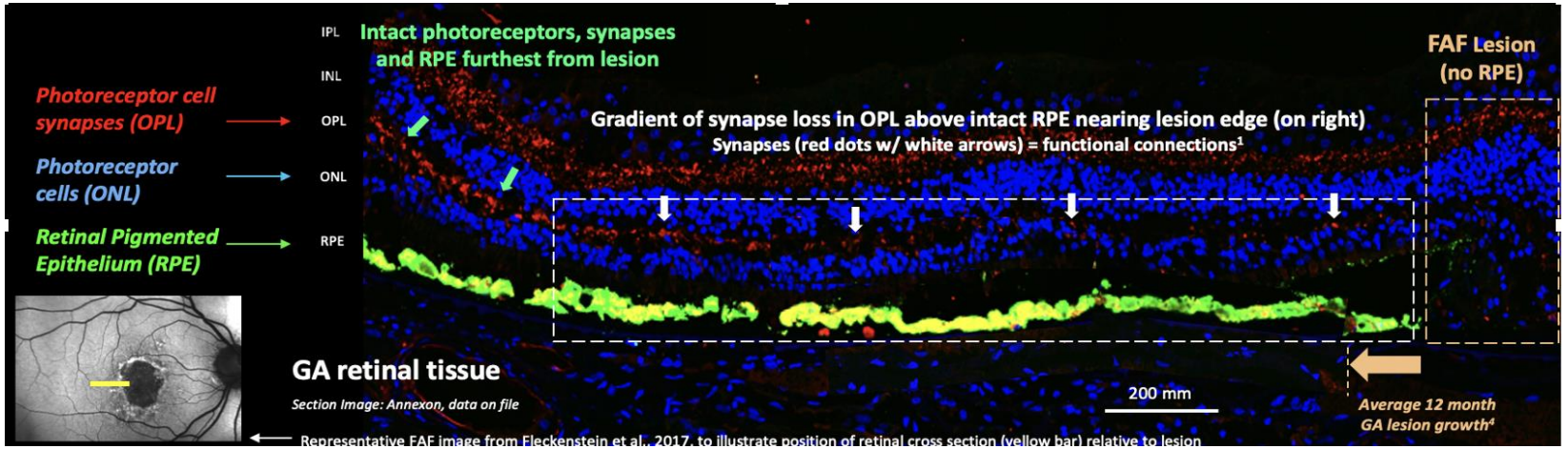
Tassoni, et al., ARVO 2024; Annexon data on file;

ANNEXON biosciences

Photoreceptor Cells and Synapses Loss Outside of GA Lesion

Human GA Retina

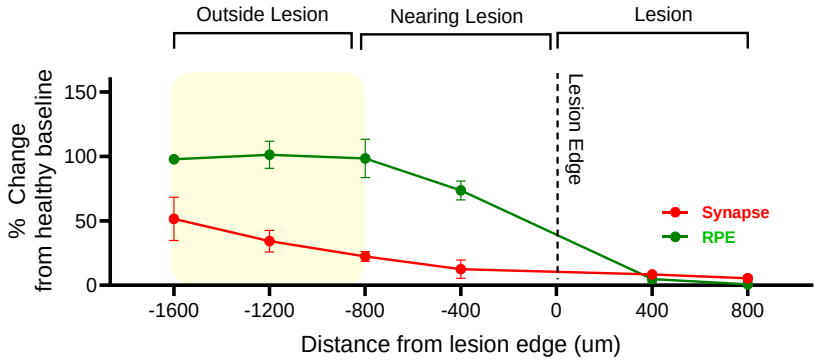
- Gradient of photoreceptor synapse and cell loss above intact RPE nearing lesion edge (white box)
- Photoreceptors are lost prior to RPE[1]; Loss of synapses is loss of function[2]
- FAF lesion growth tracks RPE loss, not photoreceptors, and correlates poorly w/ visual function[3]



Gradient of synapse loss above intact RPE nearing lesion edge

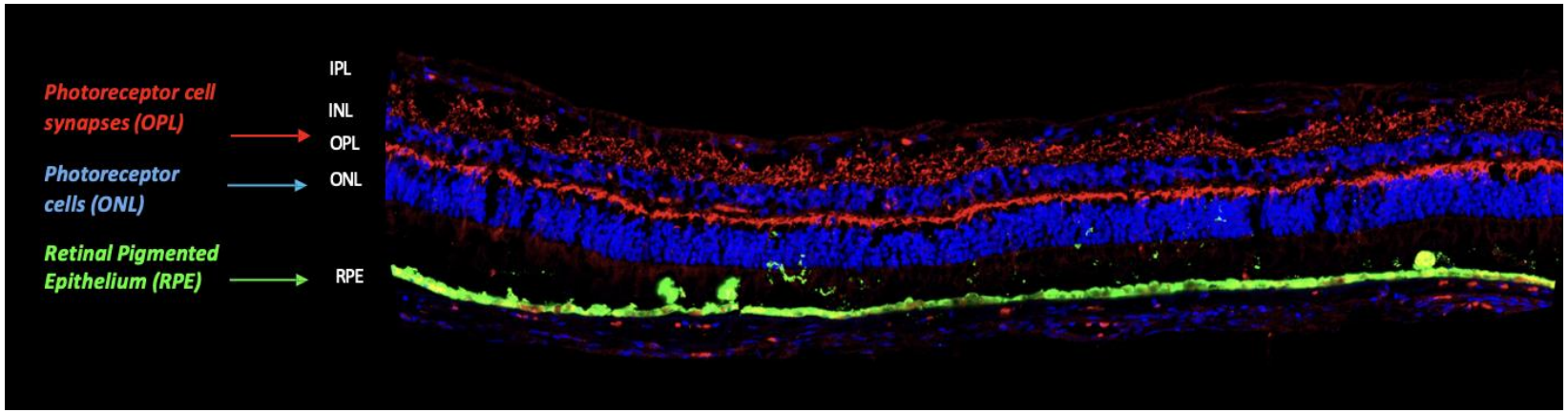
Photoreceptor Synapses
< 50% decrease outside lesion boundary

RPE cells integrity
intact in area of synaptic loss

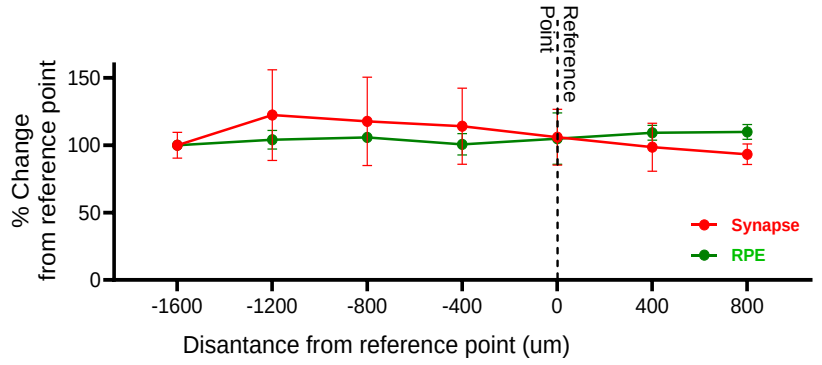


Healthy Human Retina

- Uniform layers of photoreceptor cells and synapses



Consistent synapse and RPE integrity across healthy retina



[1]Bird et al., 2014 *JAMA Ophthalmol* doi:10.1001/jamaophthalmol.2013.5799; Li, et al., 2018 *Retina* 38:1937; Pfau, et al., 2020 10.1001/jamaophthalmol.2020.2914; Sarks, et al., 1988 *Eye* 2:552; [2]Selkoe, 2002 doi: 10.1126/science.1074069; Burger, et al., doi.org/10.1016/j.ydbio.2021.04.001; [3]Heier, et al., 2020 Ophthalmology Retina **4**:673; [4]Shen, et al., 2020 *Ophthalmol Retina* **4**:899

Targeting C1q to Protect Photoreceptor Cells and Visual Function in GA

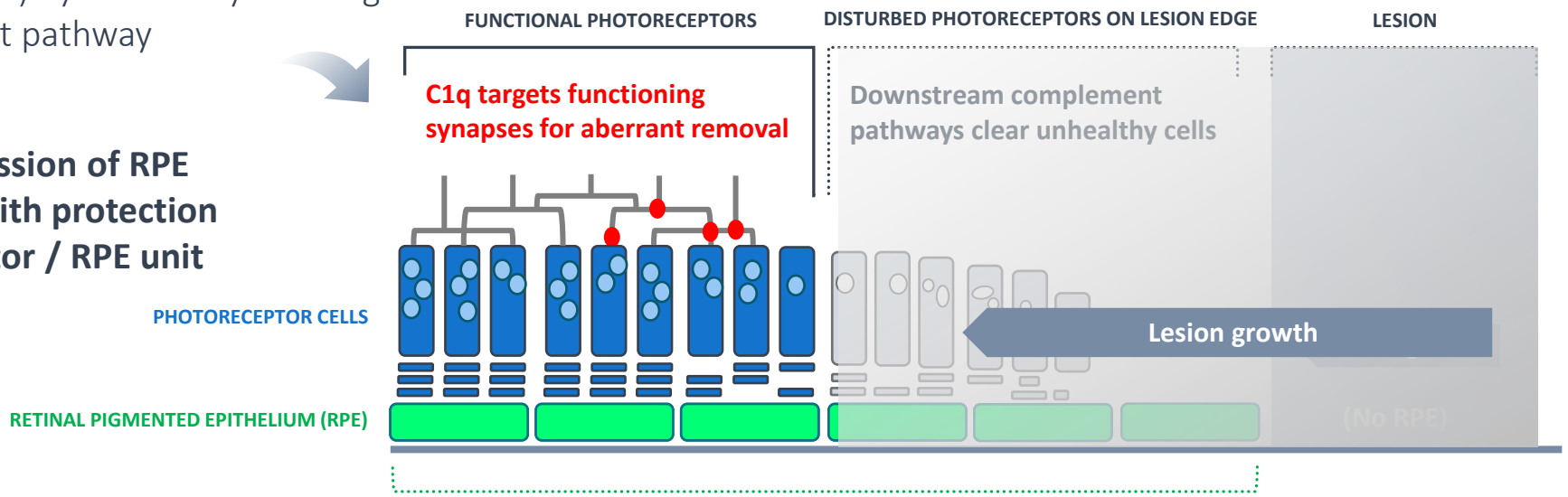
ANTI-C1q: DISTINCT NEUROPROTECTIVE MECHANISM

- Protects synapses, photoreceptor cells and decreases neuroinflammation **within the functional retina to slow vision loss**
- Beneficial impact / retinal protection increases with time
- Slow lesion growth (RPE loss) over time by protecting functional photoreceptors

Anti-C1q:
Protects the health of functional synapses **to prevent loss of visual function** (*NOT measured by FAF*) by selectively blocking the complement pathway

Removal of unhealthy, non-functional retina continues: RPE (measured by FAF) **and non-functional photoreceptors are cleared**

Further progression of RPE loss stopped with protection of photoreceptor / RPE unit



FAF measures the fluorescence of RPE cells
(independent of photoreceptor cell function)

ANNEXON biosciences

Conclusions: C1q in GA / Neurodegeneration

- **C1q-mediated synapse and neuron elimination is a common pathway in neurodegenerative disease in the central and peripheral nervous system**

- **AMD / GA** is a neurodegenerative disease, with **progressive vision loss resulting from C1q-mediated elimination of photoreceptor synapses**, and ultimately photoreceptors
  - Co-localization of C1q and photoreceptor synapses, and microglial engulfment of synapses common to animal models and human GA retina

---

- **Inhibition of C1q** in animal models of photoreceptor damage **protects from synaptic loss**, and ultimately protects photoreceptors and their function

---

- **In human GA, the loss of photoreceptors and synapses, required for vision, precedes RPE loss**
  - **Monitoring GA solely through RPE loss disconnected from visual function**

ANNEXON biosciences

ANX007: VISUAL ACUITY PROTECTION AND SAFETY IN THE PHASE 2 ARCHER TRIAL

Usha Chakravarthy, MD, PhD, CBE

Honorary and Emerita Professor of Ophthalmology and Vision Science

Queen's University of Belfast

Institute of Clinical Science

Royal Victoria Hospital, Belfast

ANX007: Inhibitor of C1q to Treat Geographic Atrophy

ANX007

IVT administered antigen-binding fragment (Fab)

KEY ATTRIBUTES

- ✓ **Design: Modeled after established IVT-administered Fab antibodies**; **same antigen recognition structure as ANX005** – full length anti-C1q antibody well tolerated as IV treatment in GBS
- ✓ **Profile:** 50kD Fab antibody; **low viscosity / non-pegylated**; <10 pM potency formulated for intravitreal administration
- ✓ **Dosing:** 5 mg / 100 microliters in Ph2; PK in patient aqueous humor supports monthly/every other month dosing; **25 microliter dose in Ph3**
- ✓ **Specificity: Full target engagement** / inhibition of C1q and the classical complement pathway observed; **lectin and alternative pathway in place** for immune and homeostatic functions[1]

[1]Sun, et al., 2023 Ophthal Sci 3(2):100290

ARCHER: Phase 2 Trial of C1q Inhibitor ANX007 in GA Patients

Randomized, double-masked
Included **foveal and non-foveal** lesions
Stratified for lesion location and lesion size
12 months (n=270)

- **Sham monthly or every other month** (n=89)
- **ANX007 5mg monthly (EM)** (n=89)
- **ANX007 5mg every other month (EOM)** (n=92)

PRIMARY BIOMARKER ENDPOINT

Change in GA lesion area as assessed by fundus autofluorescence at Month 12

PRESPECIFIED SECONDARY FUNCTIONAL ENDPOINTS

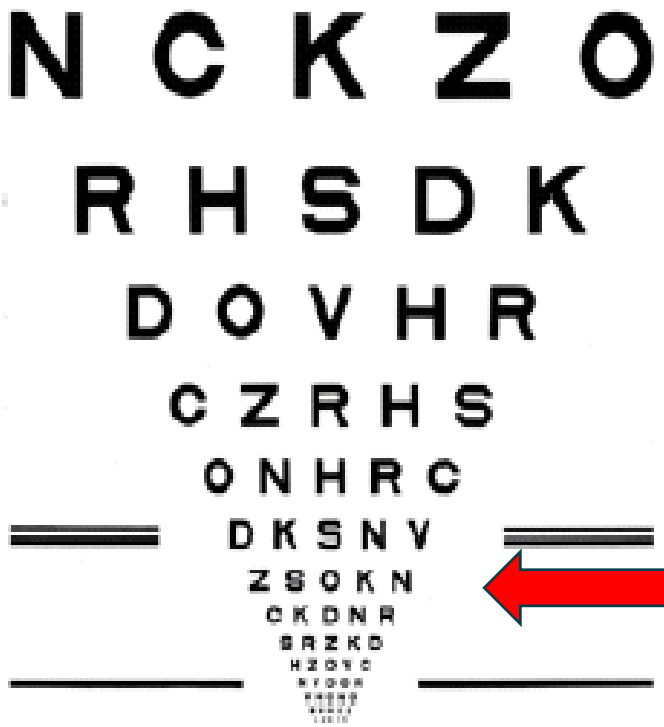
Best Corrected Visual Acuity (BCVA)
Low Luminance Visual Acuity (LLVA) & Deficit (LLVD)

Off-treatment
(6 months)

END OF STUDY
Month 18

ANNEXON biosciences

Measurements of BCVA and LLVA on ETDRS Chart at 4 Meters



55 L

70 L

30 L

ANNEXON biosciences

Patient Demographics and Study Eye Baseline Characteristics Generally Well-Balanced Across Groups

CHARACTERISTIC	SHAM POOLED (N=89)	ANX007 EM (N=89)	ANX007 EOM (N=92)
Age, mean (SD)	79.8 (7.49)	79.7 (8.64)	80.5 (8.53)
Female, n (%)	59 (66.3%)	47 (52.8%)	60 (65.2%)
Caucasian, n (%)	87 (97.8%)	87 (97.8%)	89 (96.7%)
Mean BCVA, mean (SD)	**58.5 (16.2)**	**58.8 (17.2)**	**58.3 (15.0)**
Foveal Lesion	49.4%	57.3%	53.3%
GA Lesion Size (mm^2), mean (SD)	7.28 (3.99)	7.28 (3.96)	7.53 (4.10)
GA Lesion < 7.5 mm^2	61.8%	58.4%	57.6%
Fellow Eye CNV	22.5%	24.7%	17.4%
Multifocality, n (%)	65 (73.0%)	61 (68.5%)	67 (72.8%)

ANNEXON biosciences

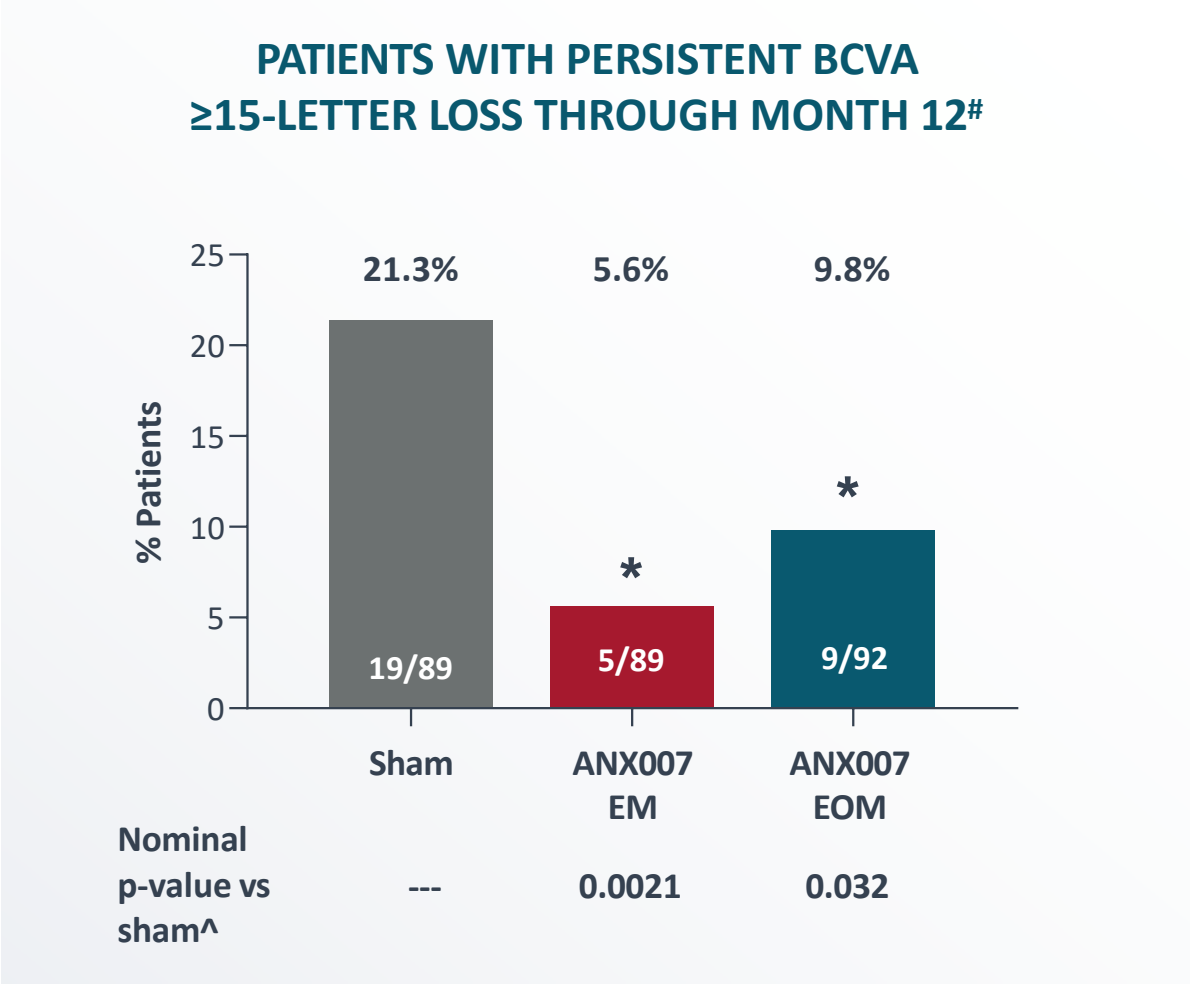
Proportion of Discontinuations Similar Among Treatment Arms and Consistent with Previous GA Studies

	SHAM POOLED (N=89)	ANX007 EM (N=89)	ANX007 EOM (N=92)
Discontinued treatment	**10 (11.2%)**	**13 (14.6%)**	**11 (12.0%)**
Withdrawal by subject			
Unrelated health issues	2	1	2
Moved / travel / time	1	2	2
Personal reasons / no reason given	2	3	2
Other	1	2	---
Death	2	2	3
Lost to follow-up	1	2	2
Physician decision	1	1	---

ANNEXON
biosciences

ARCHER TRIAL
VISUAL ACUITY RESULTS

ANX007 Demonstrated Statistically Significant Protection From Vision Loss as Measured by BCVA ≥15-Letter Loss

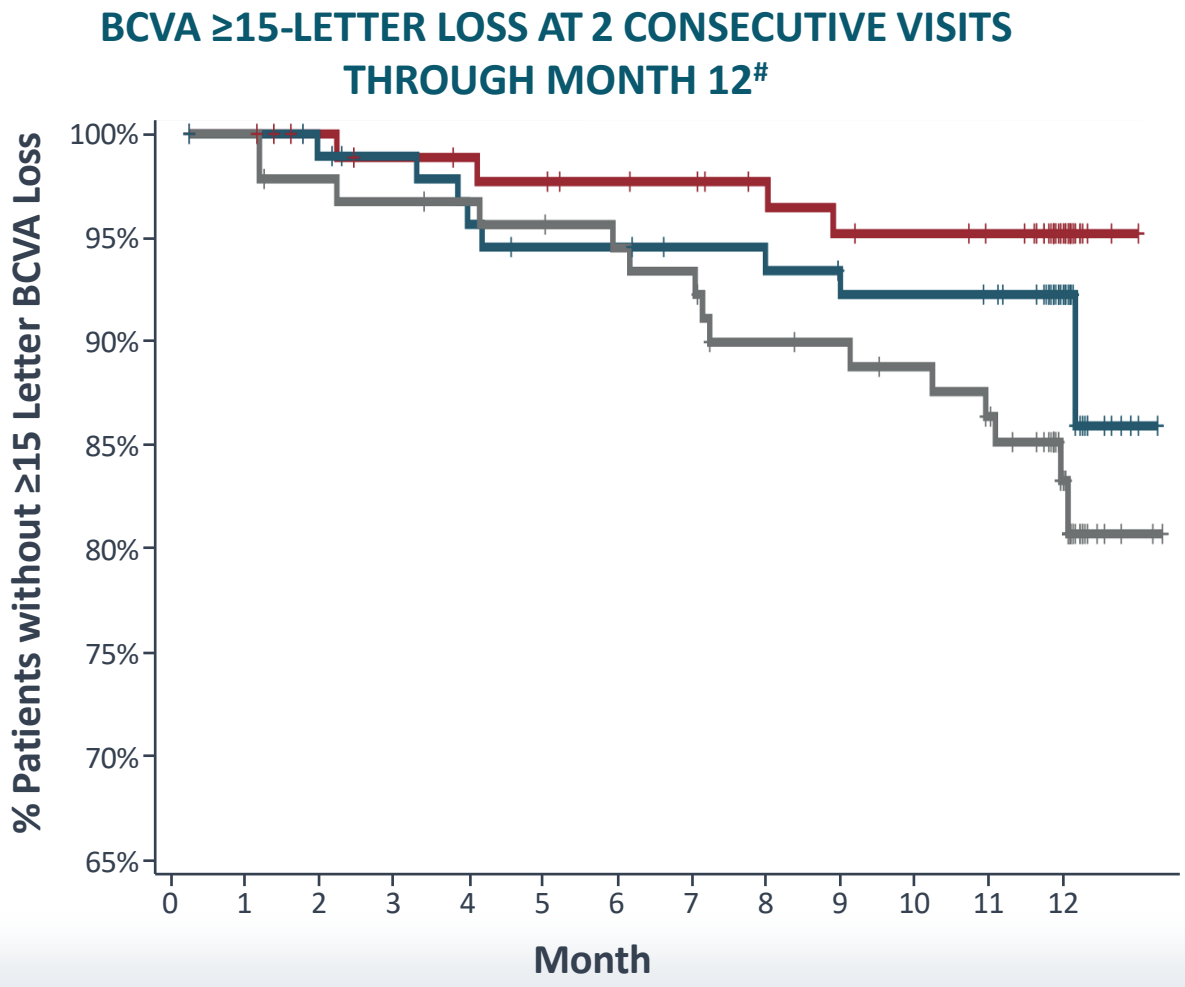


- First known significant preservation of vision in GA
- Dose-dependent response
- BCVA ≥15-letter loss universally deemed clinically meaningful
- Persistent loss defined as two consecutive visits or last visit

#Persistent for two consecutive visits through month 12 or at last study visit
^Nominal p-value from a Chi-square test in ITT population: * Nominal $p < 0.05$
Final data

ANNEXON biosciences

Significant, Time-Dependent Protection From ≥15-Letter Vision Loss with ANX007 Monthly Treatment



EM (n=89)

73% Risk Reduction ANX007 EM

HR (CI) = 0.272 (0.090 to 0.819); p = 0.0098

EOM (n=92)

50% Risk Reduction ANX007 EOM

HR (CI) = 0.504 (0.214 to 1.190); p = 0.0788

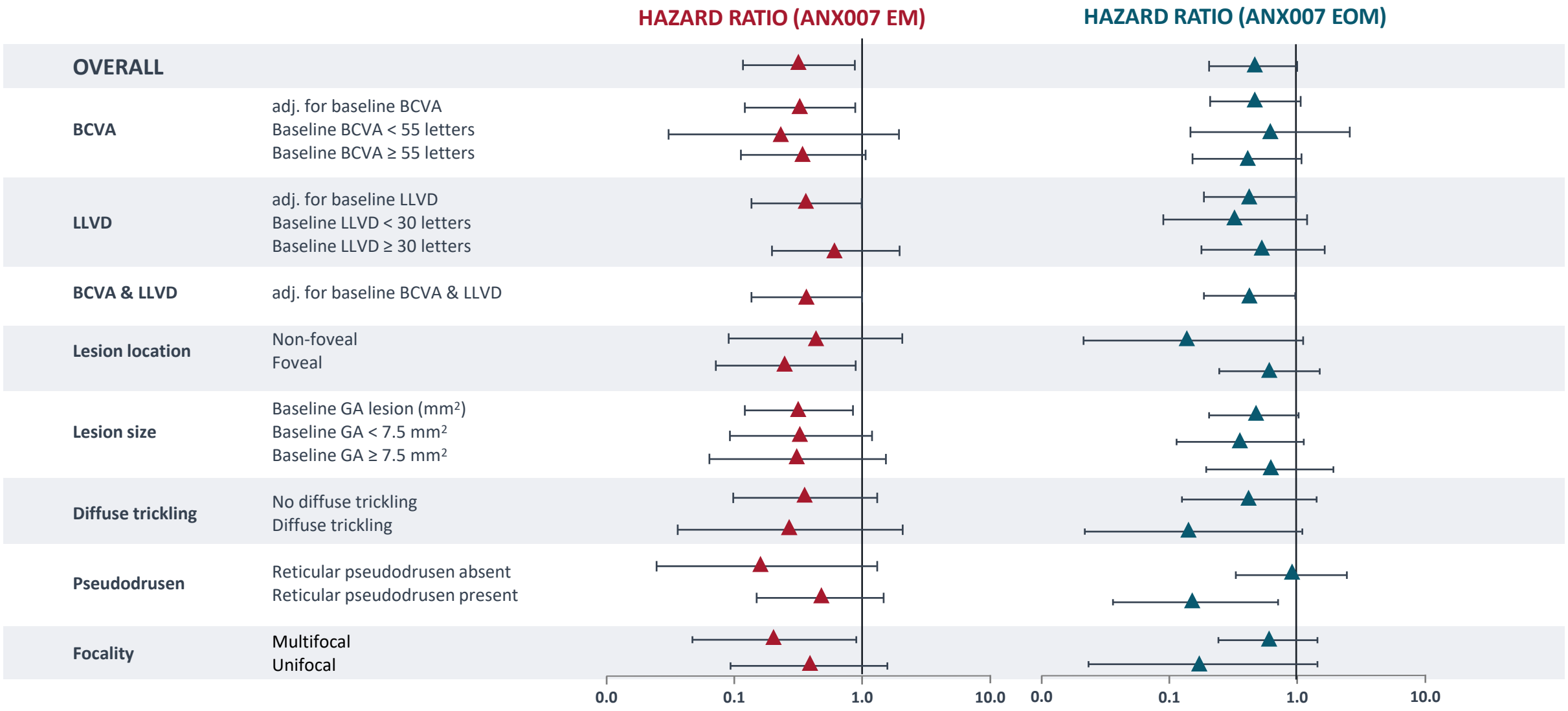
Sham (n=89)

INCREASING ANX007 IMPACT OVER TIME

HR, hazard ratio; Nominal log-rank test (versus sham) p-values are presented;
#Persistent BCVA 15-LL at two consecutive visits including month 12 supported by ensuing (off-treatment) visit
Final data

ANNEXON biosciences

ANX007 Protection from Vision Loss Consistent Across Baseline Characteristics



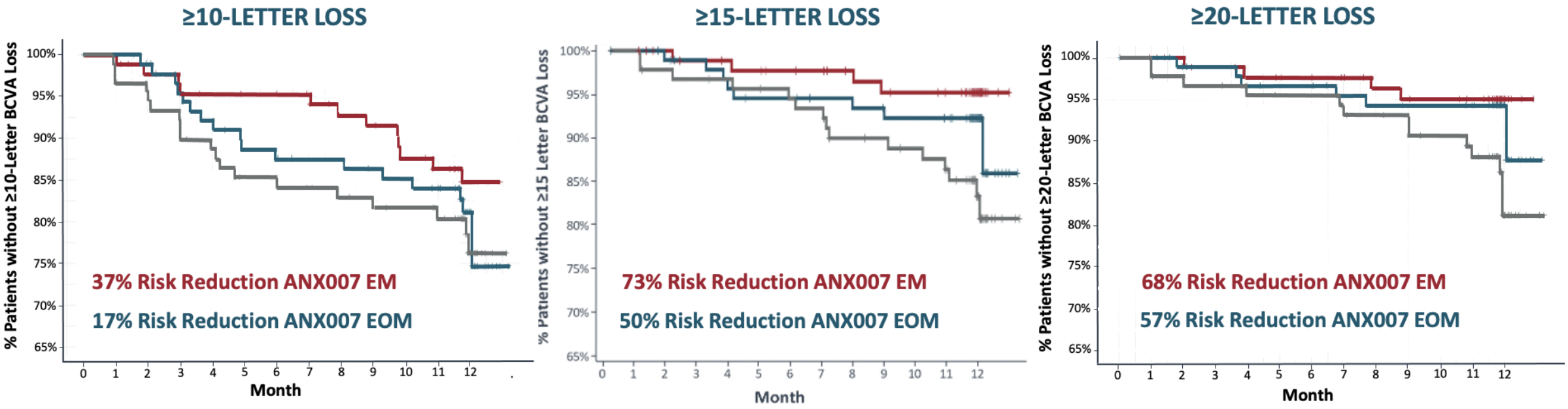
*persistent for two consecutive visits through month 12 or at last visit; Hazard ratios are from Cox regressions accounting for event time and censorship
NOTE: Hazard ratio not estimated for ANX007 EM vs Sham with baseline LLVD < 30 due to zero (0) event in ANX007 EM group for the subgroup.

ANNEXON biosciences

Consistent Protection from Vision Loss with BCVA ≥10-, ≥15- and ≥20- Letter Assessments

Significant, dose dependent protection from BCVA ≥15- and ≥20-letter loss

Persistent BCVA Vision Loss Through Month 12#

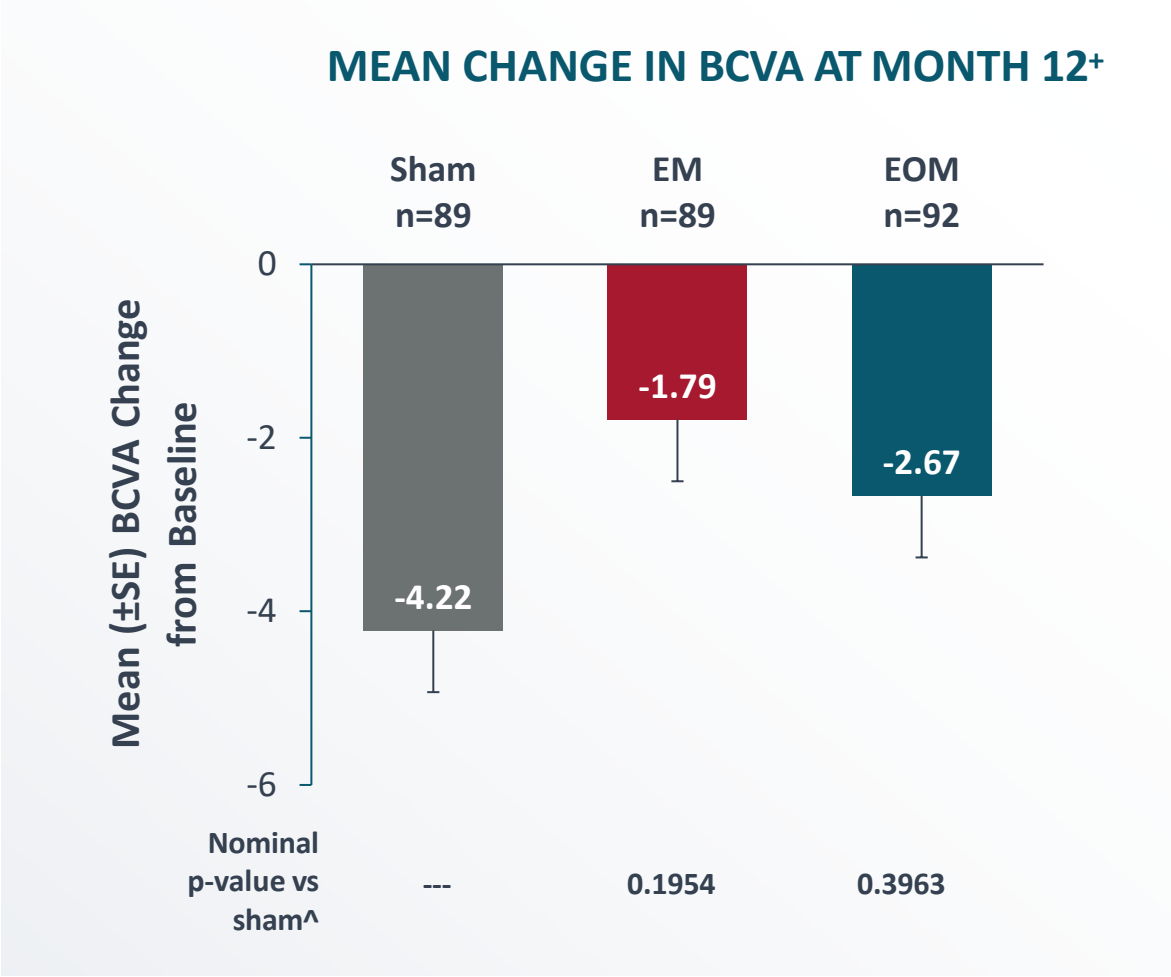


Nominal p-value vs sham^	≥10-LETTER LOSS EM	≥10-LETTER LOSS EOM	≥15-LETTER LOSS EM	≥15-LETTER LOSS EOM	≥20-LETTER LOSS EM	≥20-LETTER LOSS EOM
	0.1952	0.6015	0.0098*	0.0788	0.0330*	0.0841

#Persistent for two consecutive visits through month 12; month 12 confirmed at month 15 visit
^Nominal p-value from a Chi-square test in ITT population
* P < 0.05

ANNEXON biosciences

Mean Change in BCVA at Month 12 Further Supports Consistent Protection From Vision Loss with ANX007 Treatment



- Trend for dose-dependent response in ANX007 treated groups
- BCVA loss in sham through 12 months consistent with previous GA trials[1,2,3]

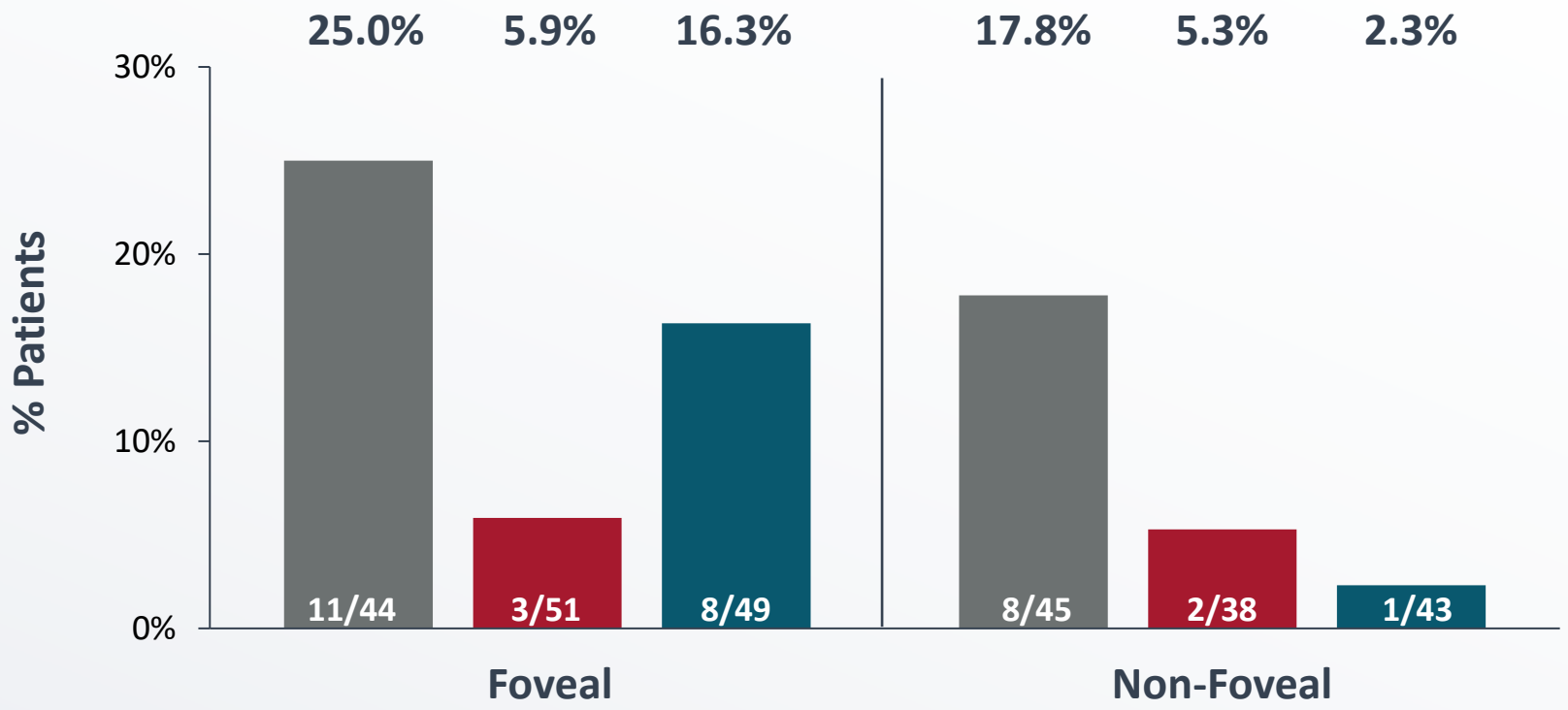
+Mean, standard error (SE), and p-value based on MMRM adjusting for baseline lesion location, lesion focality, baseline GA lesion, and the baseline GA lesion by visit interaction.
^Nominal p-value from MMRM adjusting for baseline lesion location, lesion focality, baseline GA lesion, and the baseline GA lesion by visit interaction in ITT population

[1]Liao et al (2020) *Ophthalmology* 127: 186-195; [2]Holtz et al (2018) *JAMA Ophthalmology* 136:666-677; [3]Heier et al, *Retina Society* 2022

ANNEXON biosciences

ANX007 BCVA Subgroup Analysis: Protection from Vision Loss Observed in Both Foveal and Non-Foveal Lesions

PATIENTS WITH PERSISTENT BCVA ≥15-LETTER LOSS THROUGH MONTH 12#



Nominal summary p-value vs. sham^	
ANX007 EM	0.0019
ANX007 EOM	0.0254

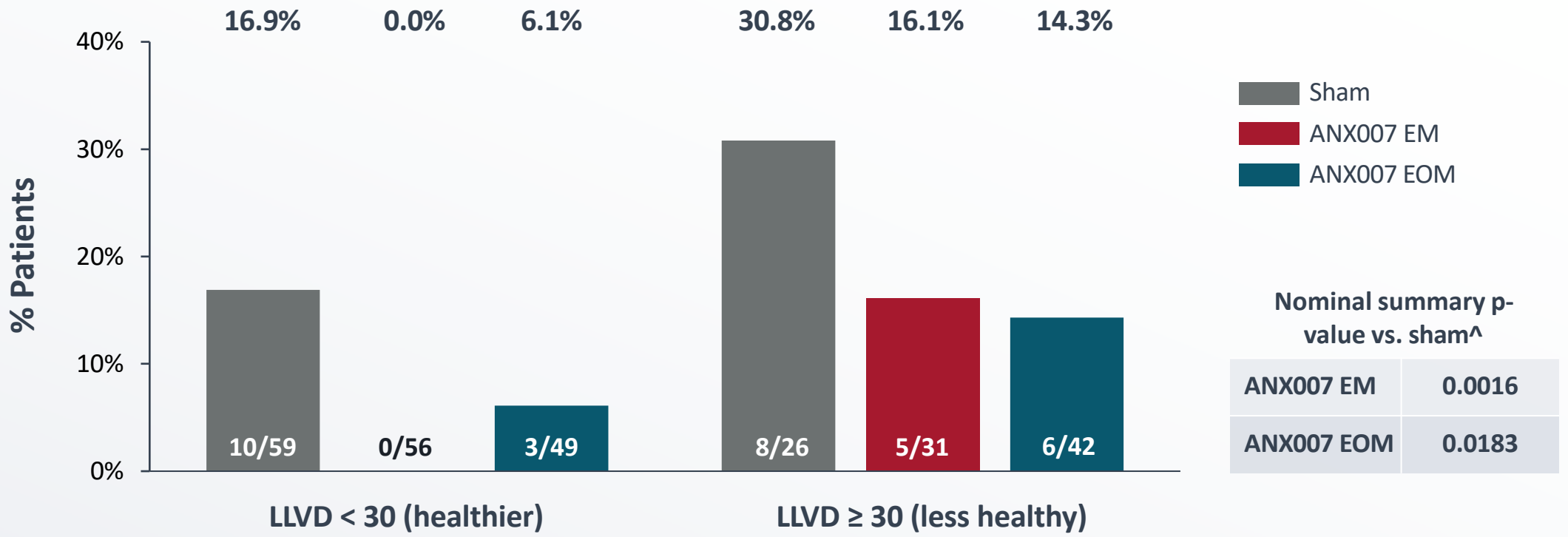
#Persistent for two consecutive visits at any time through month 12 or at last study visit
^Nominal p-value from a Cochran Mantel-Haenszel test (General Association) in ITT population
Final data

ANNEXON biosciences

Profound Effect of ANX007 in Eyes with Less Advanced Lesions

Protection from vision loss (BCVA ≥15-letter) based on retina health at baseline

PATIENTS WITH PERSISTENT ≥15-LETTER LOSS INCLUDING MONTH 12#



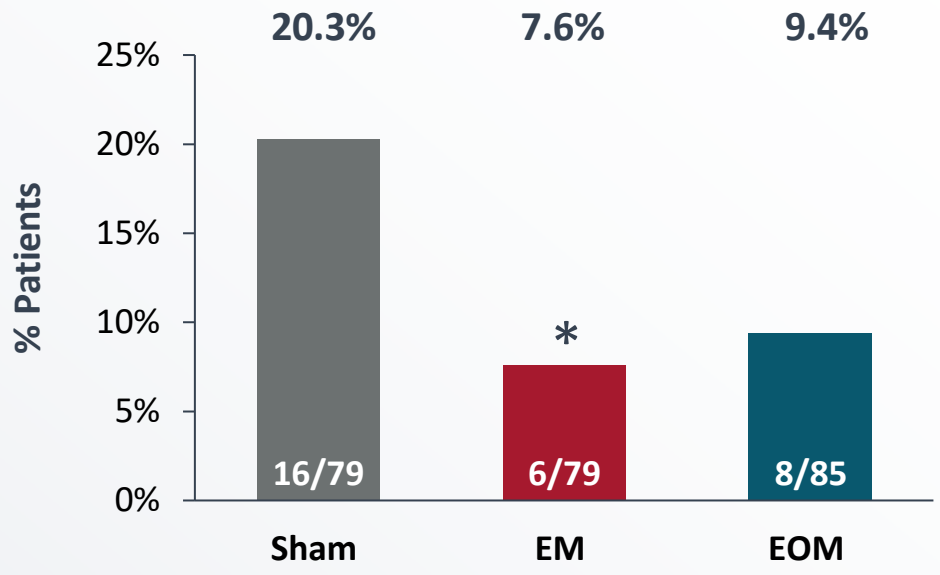
Nominal summary p-value vs. sham^	
ANX007 EM	0.0016
ANX007 EOM	0.0183

#Persistent for two consecutive visits including month 12
^Nominal p-value from a Cochran Mantel-Haenszel test (General Association) in ITT population

ANNEXON biosciences

Significant, Consistent Protection From Vision Loss with ANX007 Monthly Treatment Also Demonstrated with LLVA

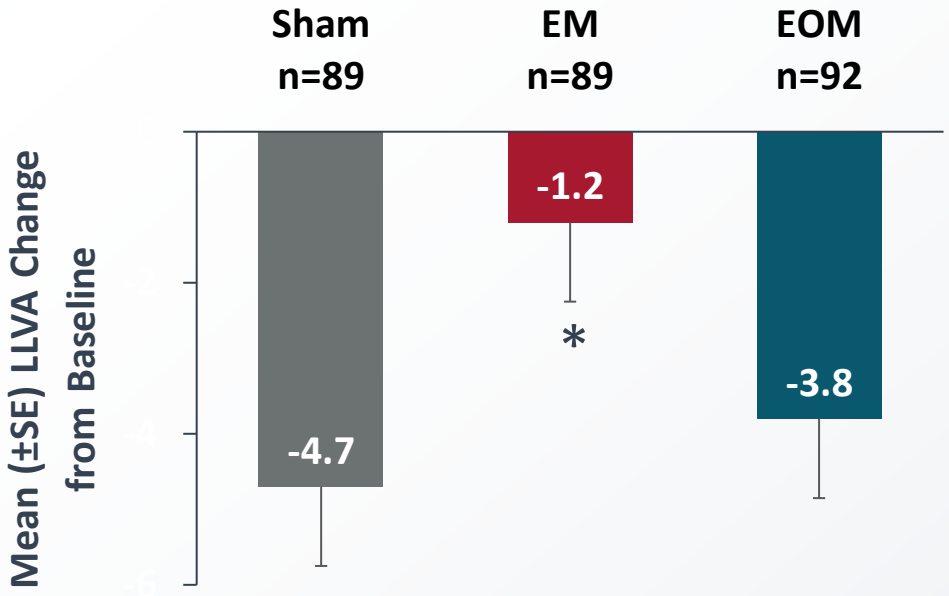
LLVA ≥15-LETTER LOSS THROUGH MONTH 12#



Nominal p-value vs Sham^	--	0.022	0.050

#Patients with single LLVA ≥15-letter loss event and at least one post-baseline LLVA measurement
^Nominal p-value from a Chi-square test
Final data

MEAN CHANGE IN LLVA AT MONTH 12+

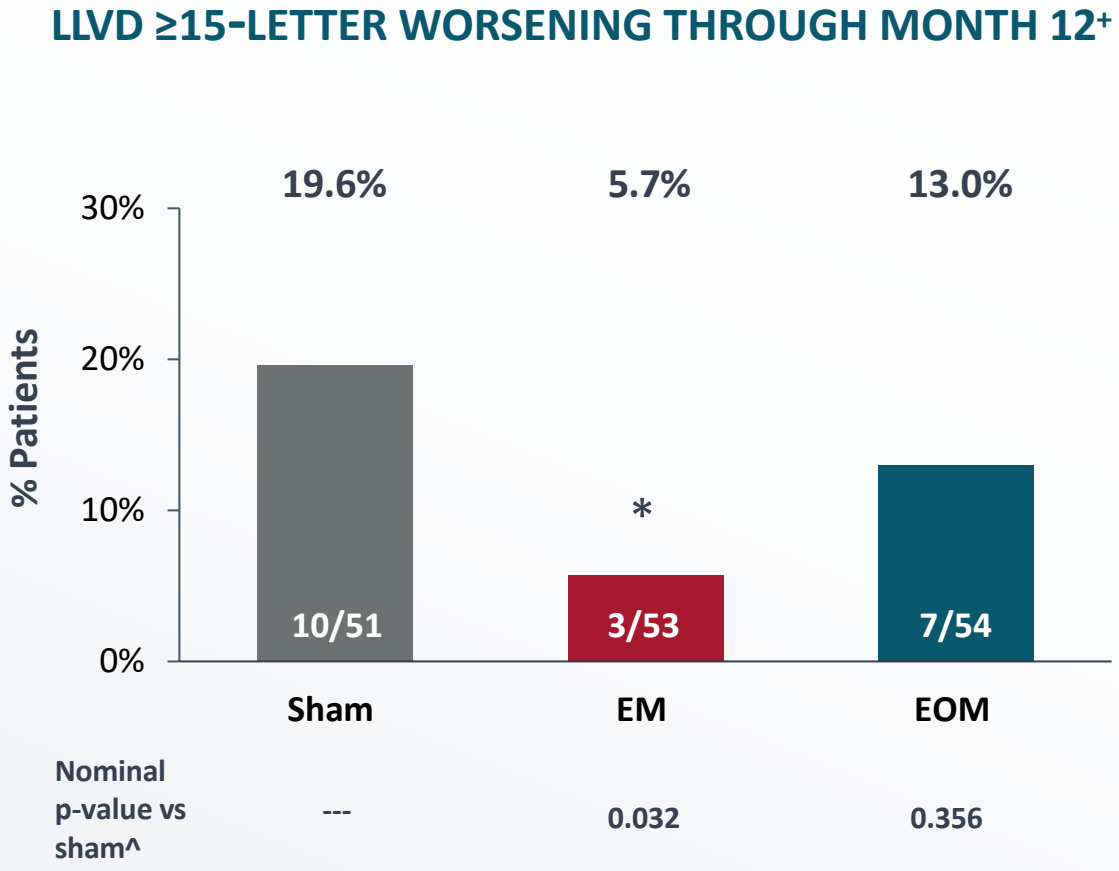


Nominal p-value vs Sham^	--	0.0354	0.5890

+Mean, standard error (SE), and p-value based on MMRM adjusting for baseline lesion location, lesion focality, baseline GA lesion, and the baseline GA lesion by visit interaction.
^Nominal p-value from a Chi-square test in ITT population
* Nominal P < 0.05
Final data

ANNEXON biosciences

ANX007 Monthly Treatment Provided Significant, Consistent Protection from Vision Loss by LLVD

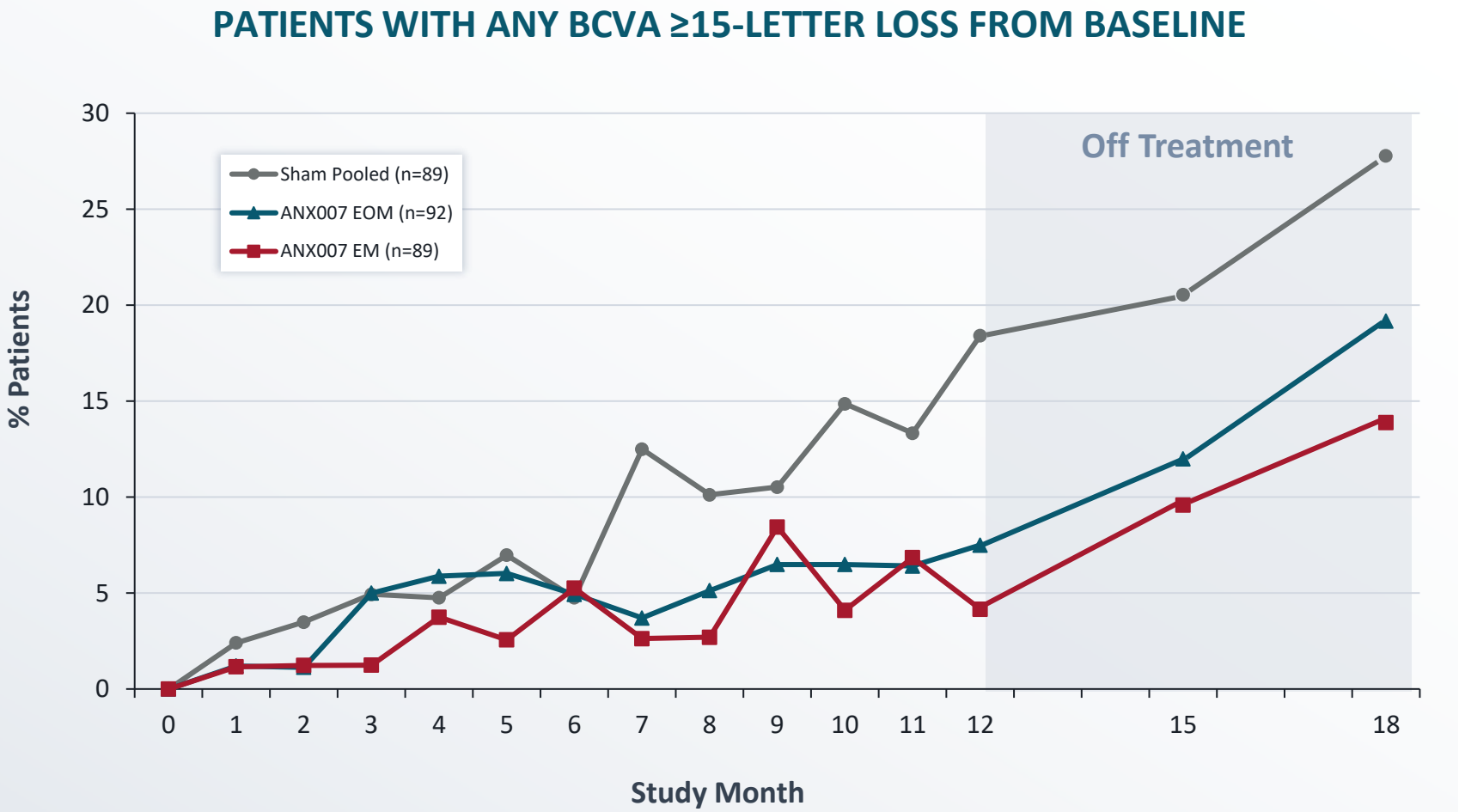


+in subjects with BCVA ≥55
^Nominal p-value from a Chi Square test
*p<0.05

ANNEXON biosciences

BCVA ≥15-Letter Loss Accelerated After Cessation of Treatment

Consistent with true on-treatment drug effect and disease-modifying mechanism of action



- Low frequency (<0.6% per month) of single BCVA ≥15-letter losses in EM- and EOM-treated groups during 12-month treatment period
- While benefit was maintained after treatment cessation the rate of BCVA≥15 LL increased to parallel that of sham (>1.6% per month)

ANNEXON biosciences

ANX007 Generally Well-Tolerated

ADVERSE EVENTS OF SPECIAL INTEREST n (%)	SHAM (N=89)	ANX007 EM (N=89)	ANX007 EOM (N=92)
Choroidal Neovascularization	3 (3.4%)	4 (4.5%)	4 (4.3%)
Endophthalmitis	0	1 (1.1%)	2 (2.2%)
Retinal Vascular Occlusion	0	0	1^ (1.1%)
Retinal Vasculitis – No Cases Reported			
Intraocular Inflammation[+]	0	2 (2.2%)	1 (1.1%)
Ischemic Optic Neuropathy[+] - No Cases Reported			

INTRAOCULAR INFLAMMATION DETAILS* n

Iritis – 1
Resolved with topical steroids in 2 days
No Vasculitis

Vitritis – 1
Resolved with topical steroids in 9 days
No Vasculitis

Vitreous Debris – 1
KP on endothelium, prior treatment with topical steroids
No Vasculitis

*Event Verbatim term listed

^Isolated cilioretinal artery occlusion; no vasculitis confirmed by DSMC and reading center
[+]Not AESI, included because of current interest

ANNEXON biosciences

Conclusions: ANX007 Protection of Visual Function in ARCHER

- In the Phase 2 ARCHER study, ANX007 monthly treatment demonstrated **consistent, significant, protection of visual function** in GA patients

  - **Risk of BCVA 15-letter loss reduced by 73%** over 12 months with ANX007 treatment
  - Protection from vision loss was **consistent across patient subgroups**, including foveal and non-foveal patients
  - Similar, **consistent protection** from vision loss seen **across multiple measures of visual acuity**, including significant slowing of loss of LLVA
  - On-drug preservation of vision supported by **return of visual function loss when ANX007 was discontinued**
  - **Most profound effects in patients with less advanced disease**

- **ANX007** treatment was **generally well-tolerated**; no CNV increase; no reported cases of vasculitis

ANNEXON biosciences

LINKING FUNCTION TO STRUCTURE: PROTECTION OF VISION-ASSOCIATED STRUCTURES WITH ANX007

Professor Paulo Eduardo Stanga, MD

Consultant Ophthalmologist & Vitreoretinal Surgeon

The Retina Clinic London, London, UK

ARCHER: Structural Findings Supporting Vision Preservation

Randomized, double-masked
Included **foveal and non-foveal** lesions
Stratified for lesion location and lesion size
12 months (n=270)

Sham monthly or every other month
(n=89)

ANX007 5mg monthly (EM)
(n=89)

ANX007 5mg every other month (EOM)
(n=92)

PRIMARY BIOMARKER ENDPOINT

Change in GA lesion area as assessed by fundus autofluorescence at Month 12

EXPLORATORY BIOMARKER ENDPOINT

Change in EZ lesion size at Month 12

PRESPECIFIED SECONDARY FUNCTIONAL ENDPOINTS

Best Corrected Visual Acuity (BCVA)
Low Luminance Visual Acuity (LLVA) & Deficit (LLVD)

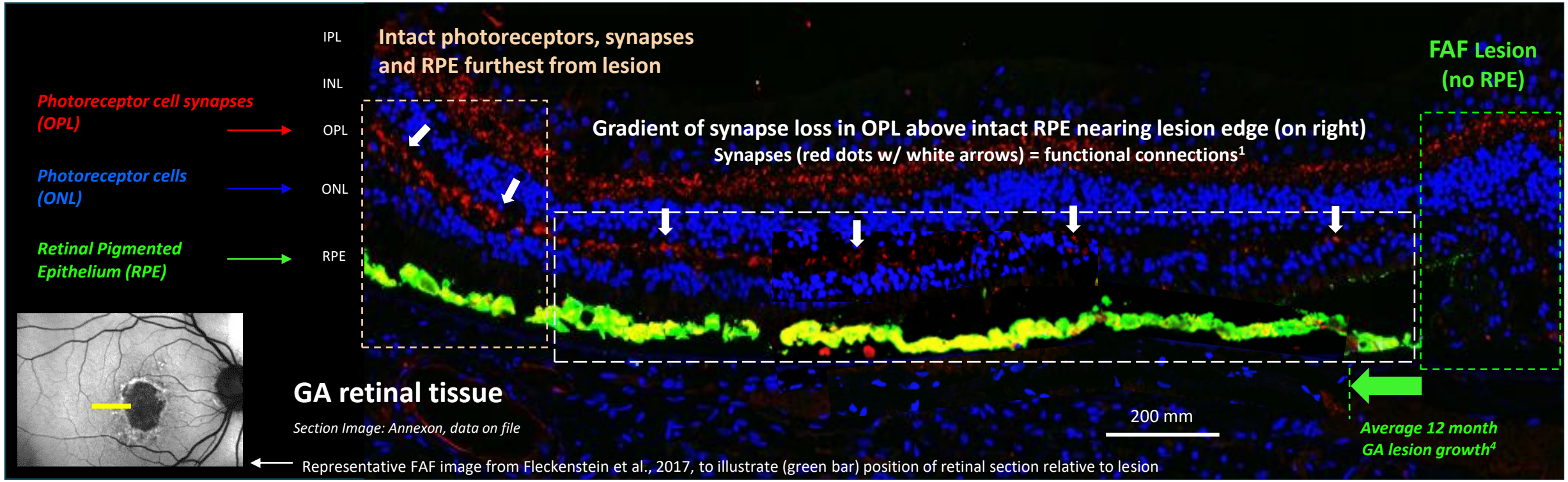
Off-treatment
(6 months)

END OF STUDY
Month 18

ANNEXON biosciences

Loss of Photoreceptor Synapses Precedes Loss of RPE

- Photoreceptor cells and their synapses are lost over intact RPE (white box)
  - Decreasing gradient of red-labeled photoreceptor synapses moving toward the lesion on right - loss of synapses is loss of function[1]
  - Also, decreasing gradient of blue-labeled photoreceptor cells toward lesion – photoreceptors are lost prior to RPE[2]
- FAF measures RPE loss/lesion growth, but not photoreceptor or synapse / cell loss and correlates poorly w/ visual function[3]

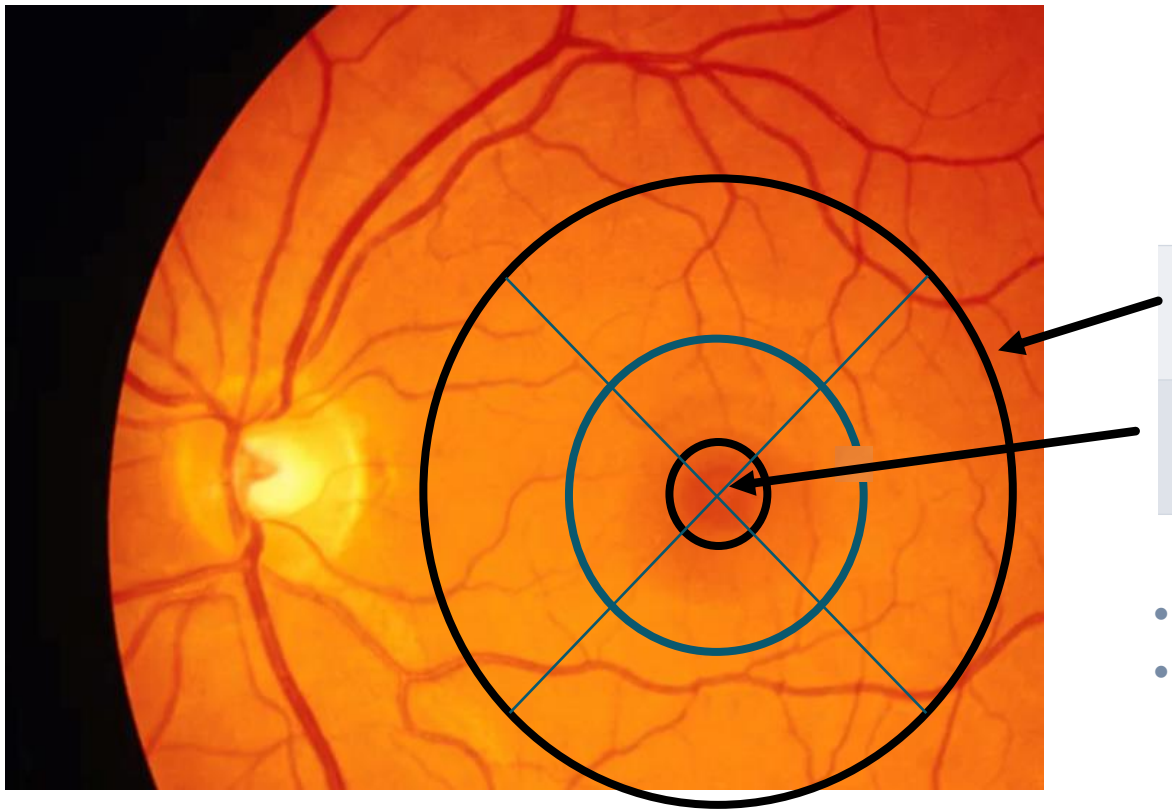


[1]Selkoe, 2002 doi: 10.1126/science.1074069; Burger, et al., doi.org/10.1016/j.ydbio.2021.04.001; [2]Bird et al., 2014 *JAMA Ophthalmol* doi:10.1001/jamaophthalmol.2013.5799; Li, et al., 2018 *Retina* 38:1937; Pfau, et al., 2020 10.1001/jamaophthalmol.2020.2914; Sarks, et al., 1988 *Eye* 2:552; [3]Heier, et al., 2020 Ophthalmology Retina **4**:673; [4]Shen, et al., 2020 *Ophthalmol Retina* **4**:899

ANNEXON biosciences

Broad RPE Loss Does Not Correlate Well with BCVA Loss[1]

RPE loss in central 1mm shows better correlation to BCVA loss, and as early as 6 months



SPEARMAN CORRELATION COEFFICIENTS COMPARING THE CHANGES IN RPE AREA WITH BCVA CHANGE OVER TIME

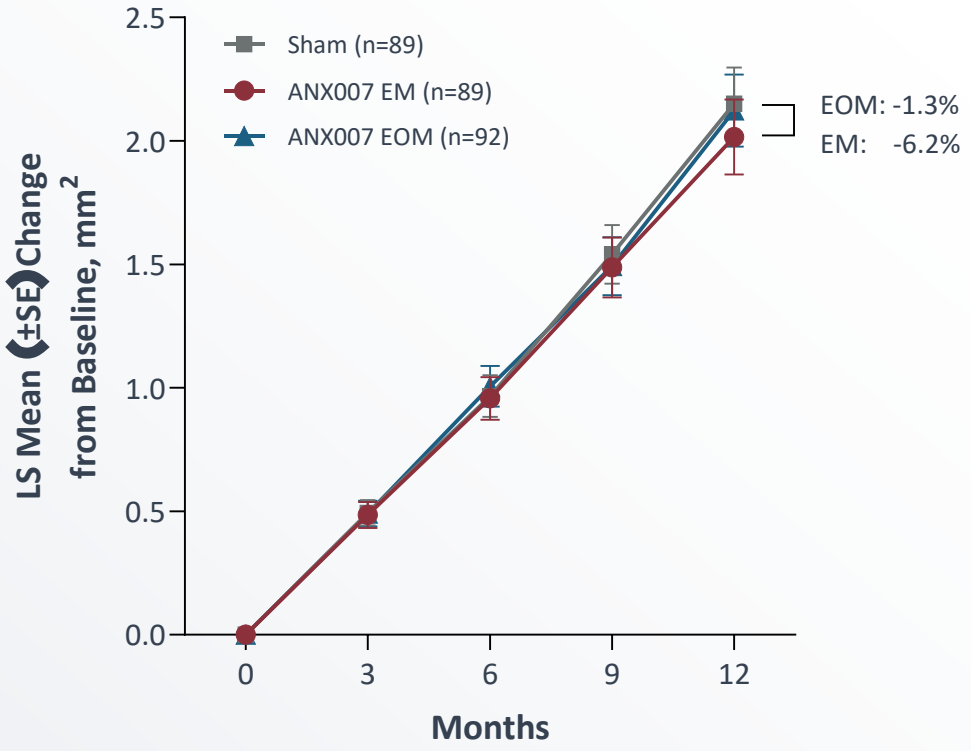
Location	Month 6	Month 12	Month 18
Full 6 mm diameter	r=0.11 p=0.54	r=0.24 p=0.15	r=0.37 **p=0.03**
1mm foveal center	**r=0.37** **p=0.03**	**r=0.51** **p=0.001**	**r=0.61** **p<0.0001**

- Correlation in central 1mm significant as early as 6 months
- Overall lesion growth significantly correlates after 18 months

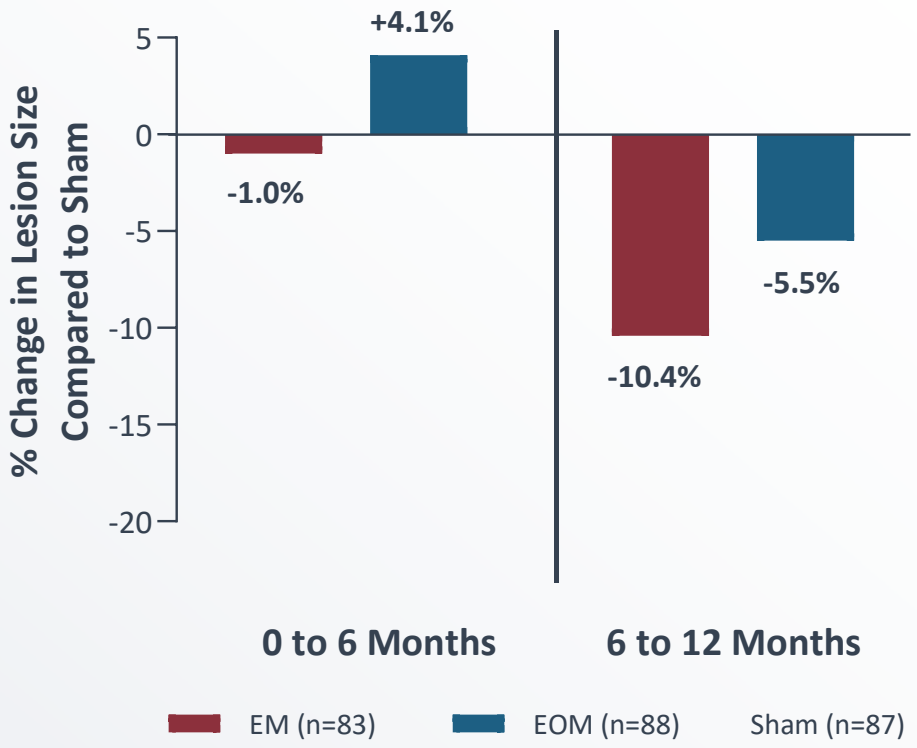
1. Adapted from Sayegh et al, Am J Ophthalmology 2017 179:118-128

ANX007 Did Not Significantly Reduce RPE Biomarker Loss Across Full Retina, but Effects Increased Over Time

RPE LOSS FROM BASELINE TO MONTH 12#



CHANGE IN RPE LOSS OVER TIME#



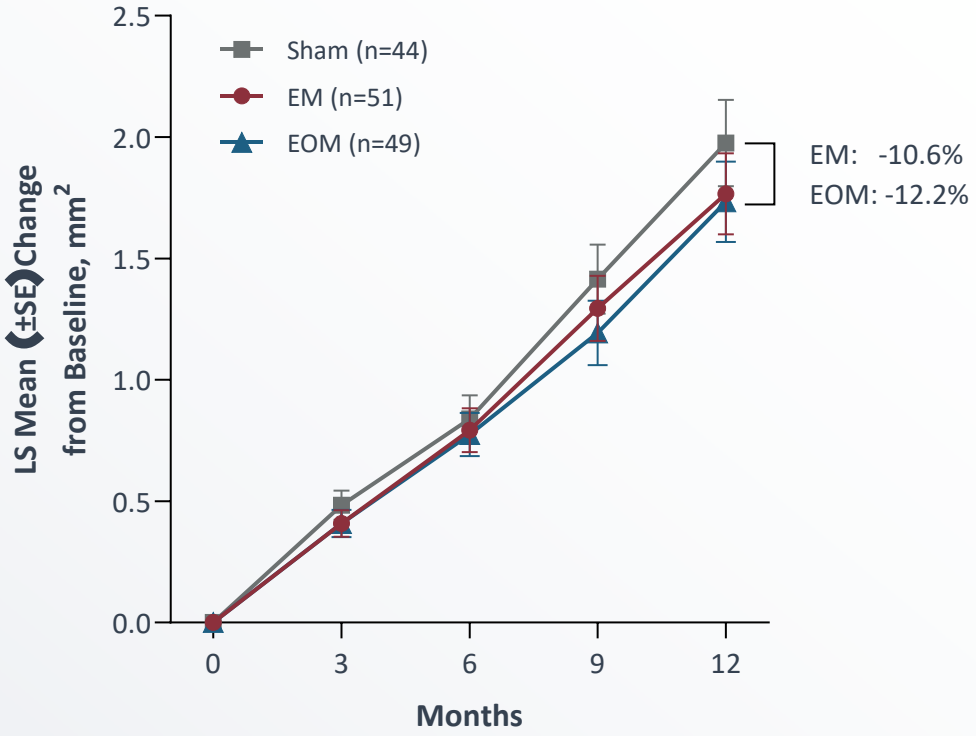
#Least-square (LS) mean and its standard error (SE) are based on a mixed-effect model for repeated measures (MMRM) adjusting for baseline lesion location, lesion focality, baseline GA lesion, and the baseline GA lesion by visit interaction.

ANNEXON biosciences

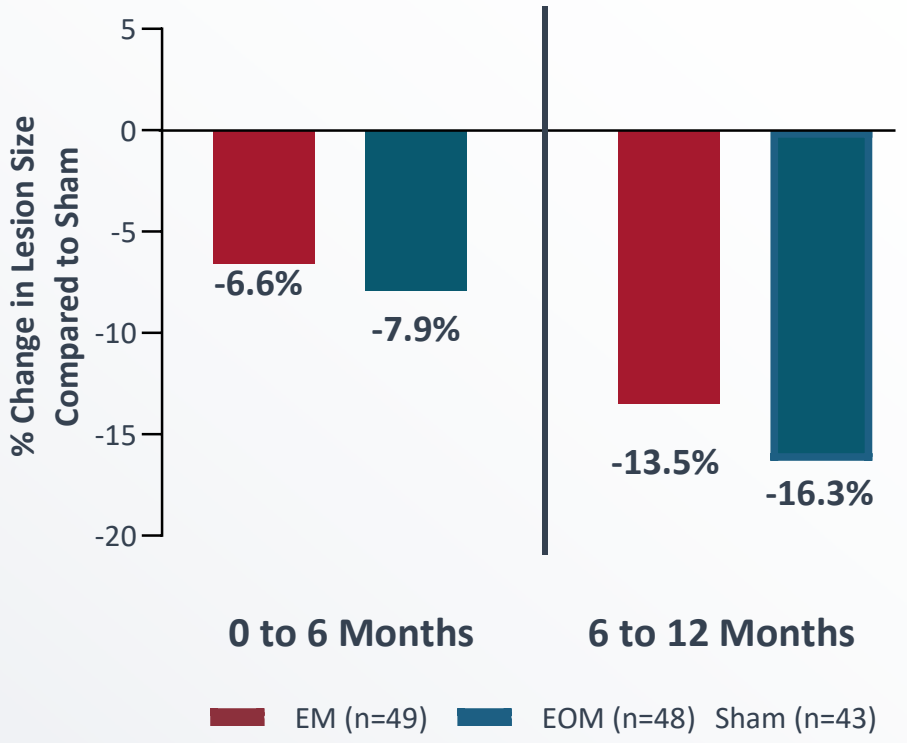
Differential Effect on RPE Biomarker Loss in Patients with Foveal Involvement at Baseline

Greater protection of RPE in region responsible for visual acuity

RPE LOSS FROM BASELINE TO MONTH 12[#]
FOVEAL PATIENTS



CHANGE IN RPE LOSS OVER TIME[#]
FOVEAL PATIENTS

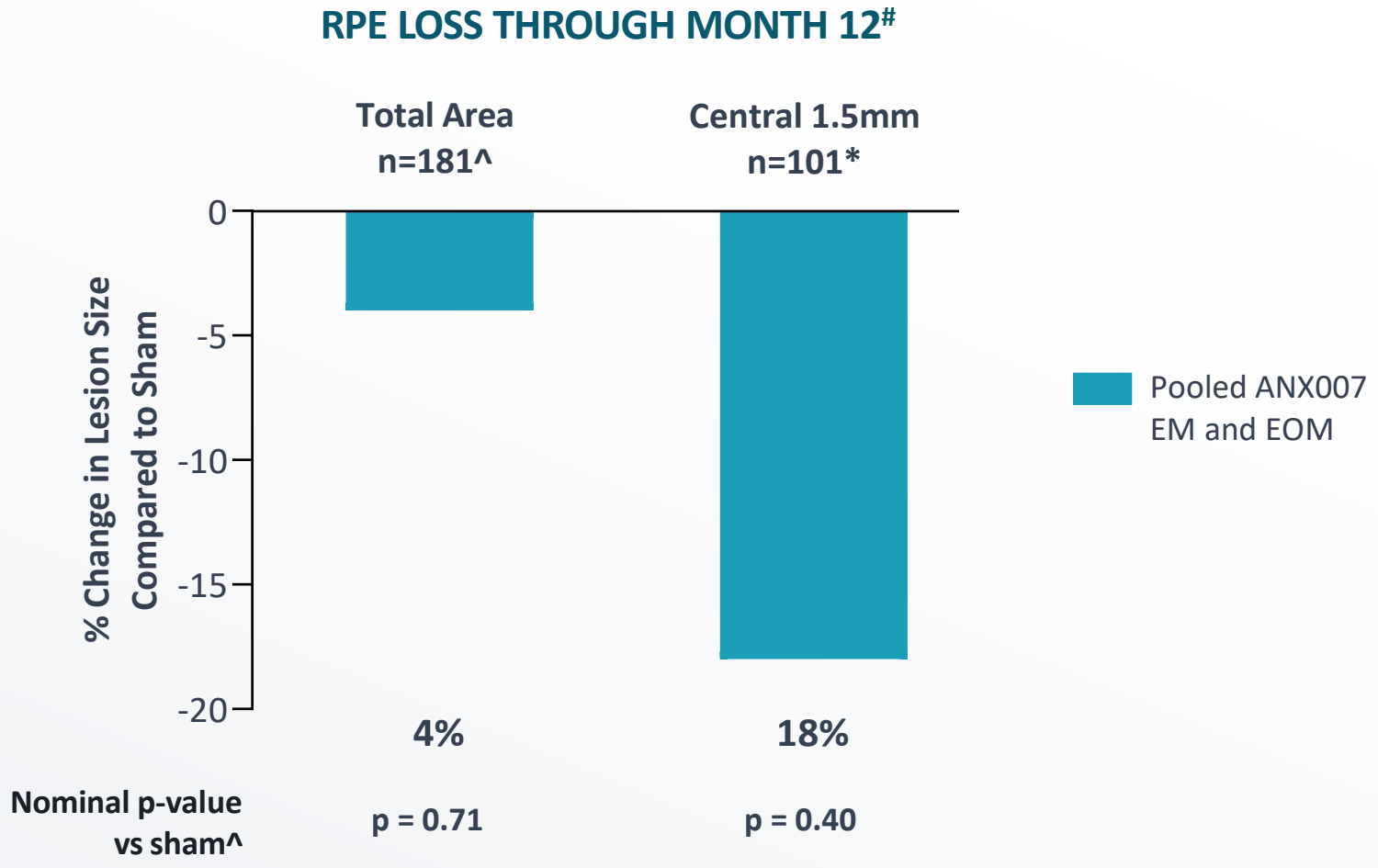


[#]Least-square (LS) mean and its standard error (SE) are based on a mixed-effect model for repeated measures (MMRM) adjusting for baseline lesion location, lesion focality, baseline GA lesion, and the baseline GA lesion by visit interaction.

ANNEXON biosciences

ANX007 Protection from RPE Loss More Robust in 1.5 mm Foveal Center

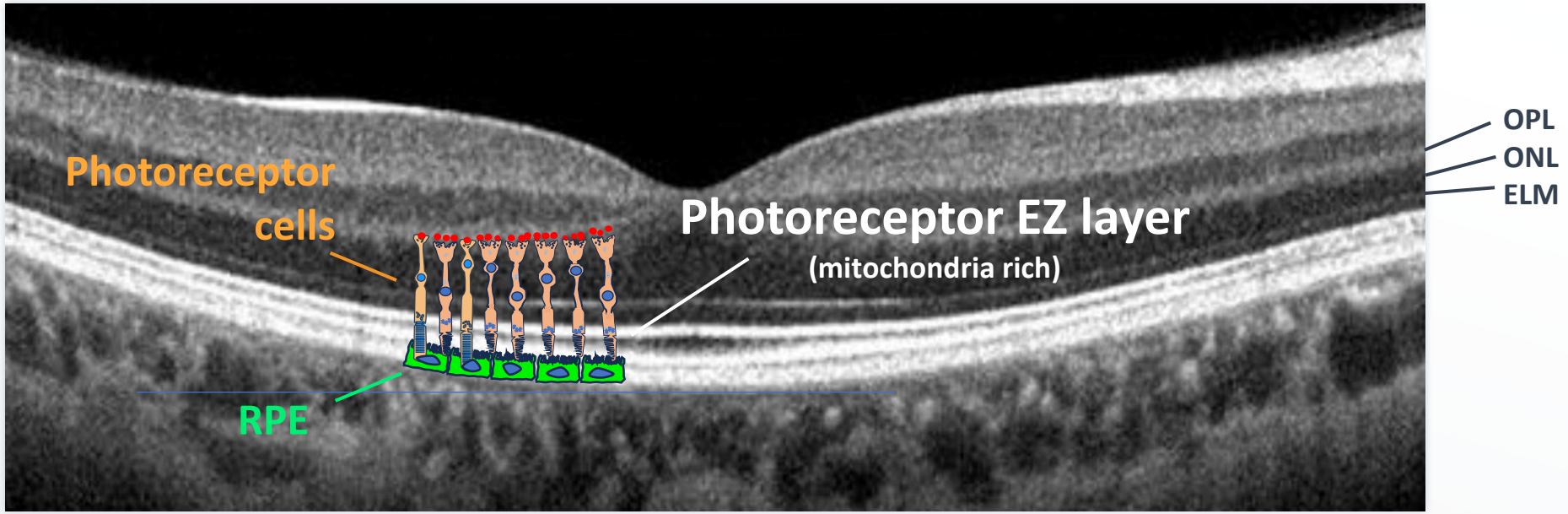
Consistent with treatment that protects from vision loss



#From a mixed model for repeated measures (MMRM) analysis; ^ITT population
*Heidelberg Spectralis OCT population with baseline OCT data, excludes patients with >98% atrophy at baseline

ANNEXON biosciences

Ellipsoid Zone (EZ) Biomarker Directly Measures Photoreceptor Anatomy: More Proximal to ANX007 Synapse Protection MOA



octscans.com

ARCHER EZ POPULATION

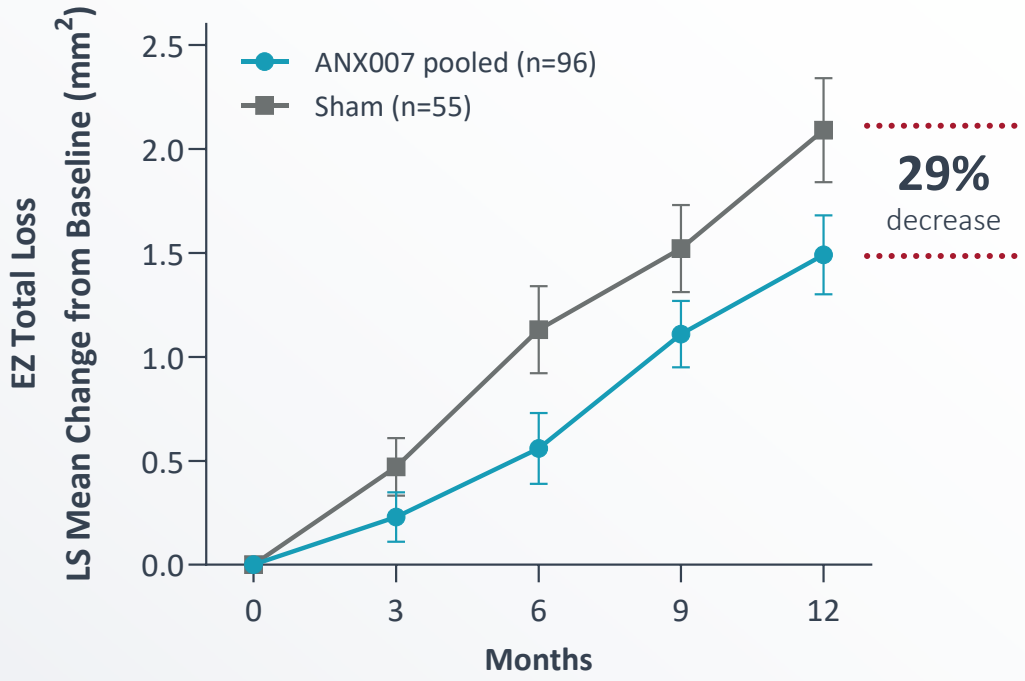
Sham	ANX007 EM	ANX007 EOM	Total
71	60	62	193

- 193 patients with OCT scans from Heidelberg Spectralis
- Patient demographics and study eye characteristics were generally well balanced across groups
- Same treatment effect between sham, EM and EOM groups as in whole study population

ANNEXON biosciences

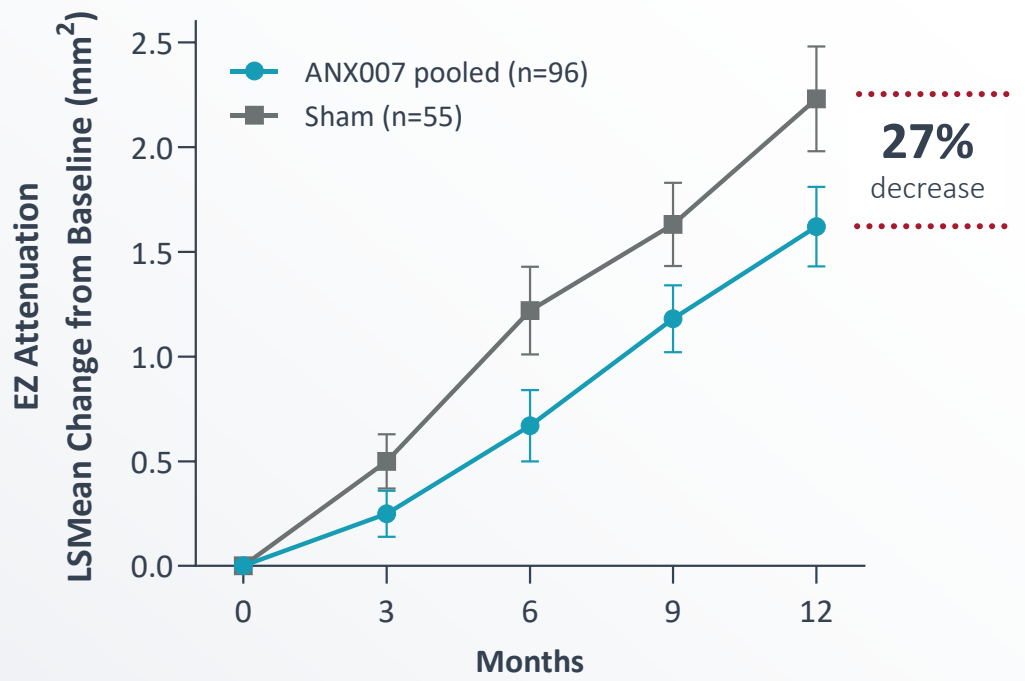
ANX007 Significantly Protected Photoreceptors Across Retina Through 12 Months

EZ TOTAL LOSS (EZ = 0 µm thickness)*



Nominal p-value vs sham^ ANX007 0.017

EZ ATTENUATION (EZ < 20 µm thickness)*



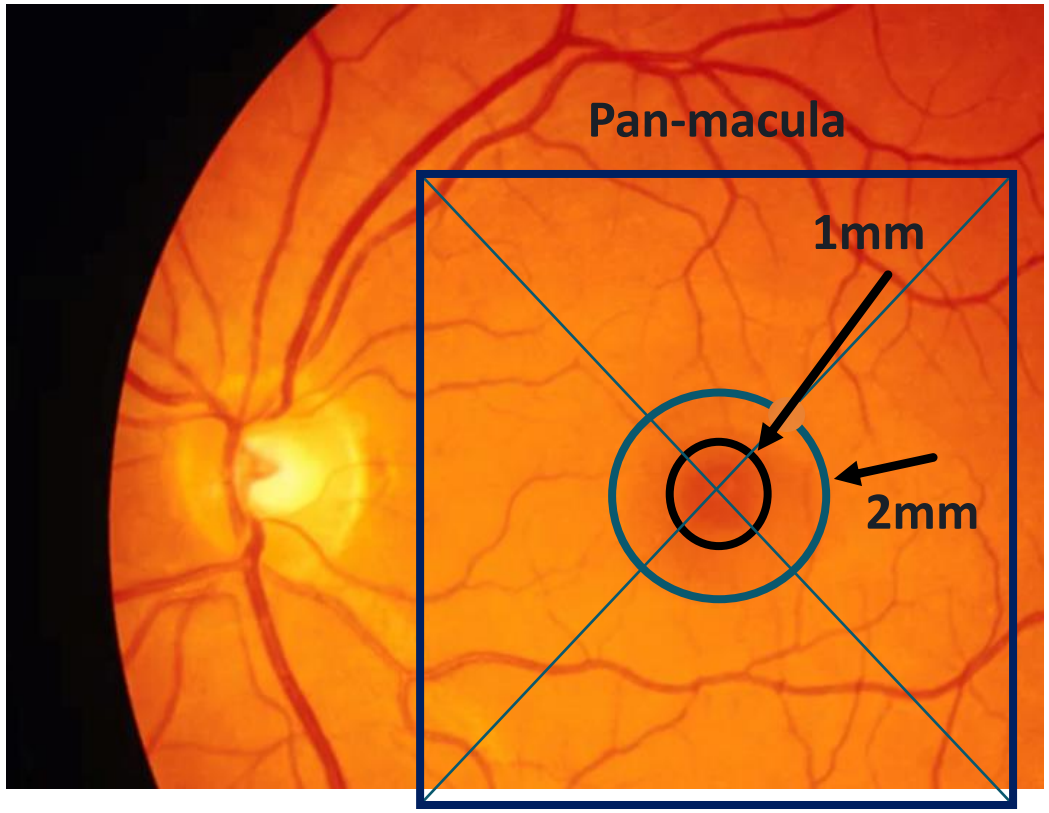
Nominal p-value vs sham^ ANX007 0.021

^Nominal p-values from a mixed model for repeated measures (MMRM) analysis; Heidelberg Spectralis OCT population with baseline OCT data (n=151)
*Two treatment groups (EM and EOM) were not different statistically

ANNEXON biosciences

EZ Disruption in Central Fovea, Not Across Full Retina, Correlates with BCVA in GA Patients^

Foveal center subdomain: region with higher density of synapses and responsible for visual acuity



Parameter	Region	Correlation with GA Eyes (Pearson r value)
EZ Loss	1mm	**-0.49***
	2mm	**-0.54***
	Pan-macula	-0.34 (ns)

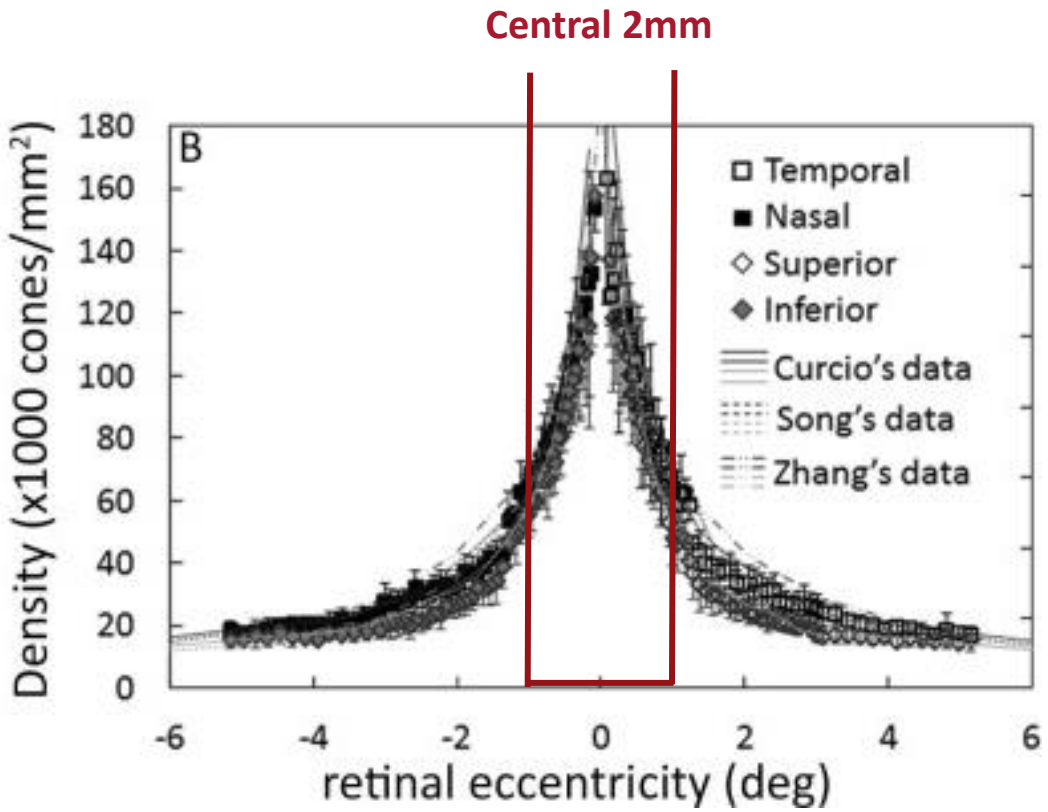
*p≤0.05

^From Yordi et al (2024) J Pres Med 14: 543

ANNEXON biosciences

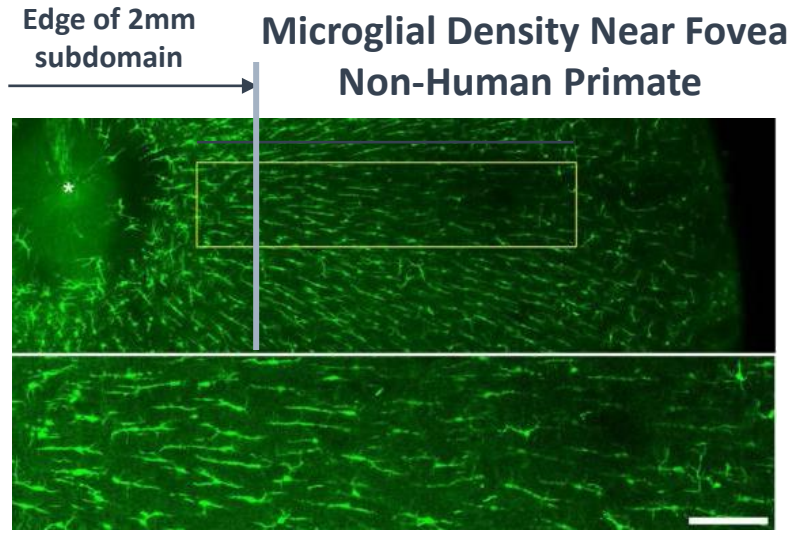
Cone and Microglia Densities Peak at the Fovea

Average Cone Density Across Retina Greatest With Central 2mm Subdomain



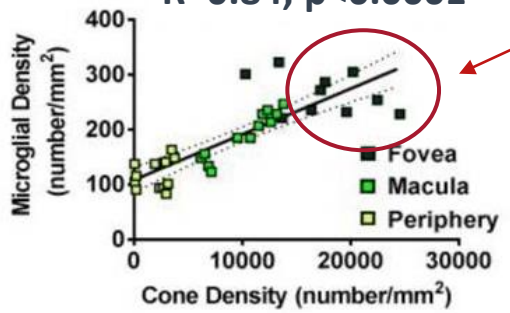
Sawides et al Vision Research, Volume 132, March 2017, Pg 34-44

Density of Microglia, C1q Effector Cell, Higher Near Central 2mm Subdomain



Correlation to Microglial Density in OPL

R=0.84, p<0.0001



Increased cones density associated to increased microglia in OPL

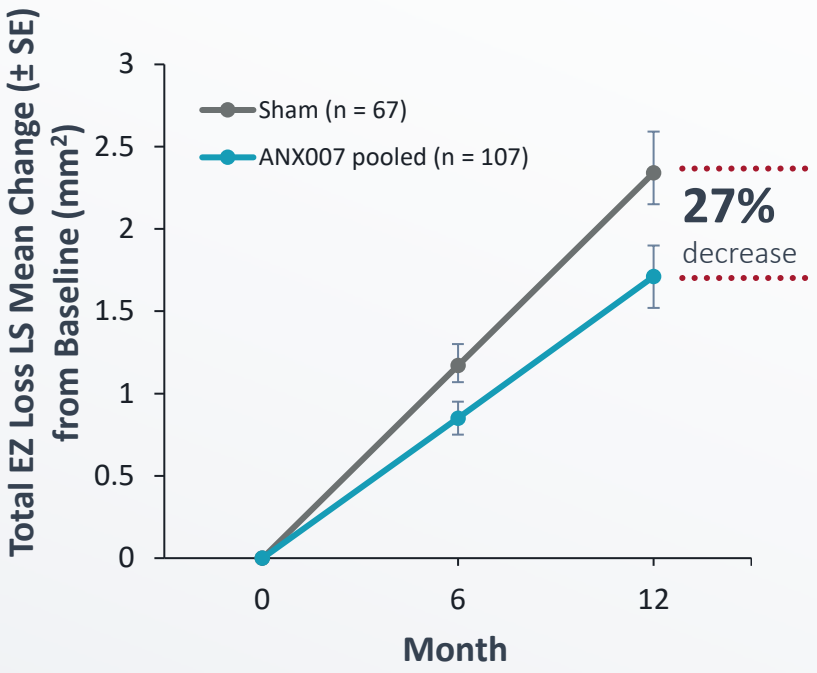
Sinagravelu J, eta al. Brain Struct Funct. 2017

ANNEXON biosciences

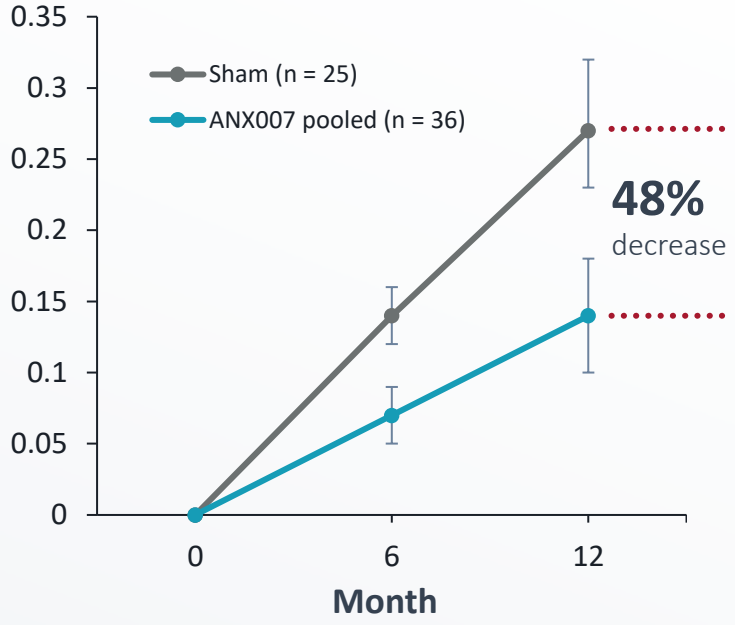
Photoreceptor Protection Through 12 Months in Central Fovea

More robust protection with ANX007 in center, area best associated with vision, compared to pan-macula

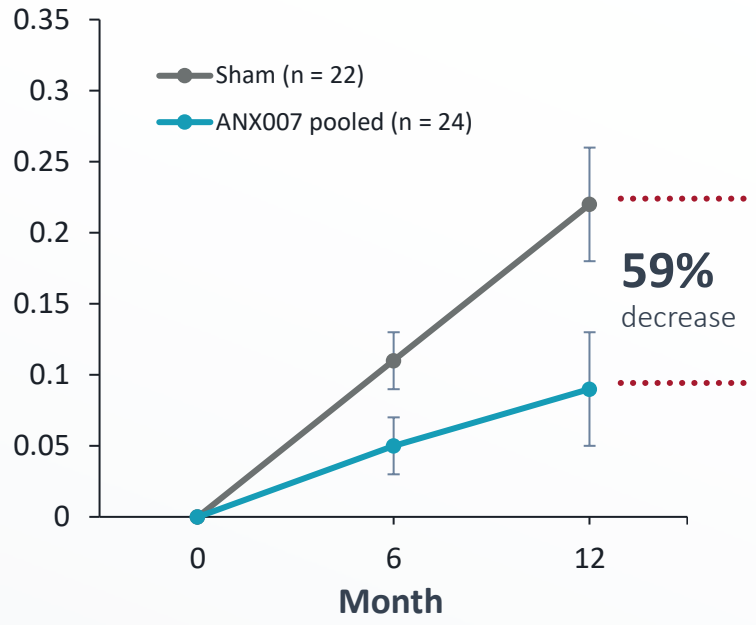
PAN-MACULA



CENTRAL 2.0 MM



CENTRAL 1.5 MM



Nominal p-value^		
	ANX007 Pooled vs Sham	0.0457
	ANX007 Pooled vs Sham	0.0218
	ANX007 Pooled vs Sham	0.0319

^Nominal p-values from a linear mixed model for repeated measures model (slope) analysis;
Heidelberg Spectralis OCT population with baseline OCT data, excludes patients with >98% atrophy/attenuation at baseline

ANNEXON biosciences

Conclusions: ANX007 Protection of Vision-Associated Retina Structures in GA

- ANX007 protection from loss of RPE increases with time
- Greater ANX007 protection of RPE in central structures associated with vision loss
- Significant protection of photoreceptors, structures more proximal to ANX007's synaptic protection MOA
- Greatest protective effect of ANX007 in central subdomains associated with vision

ANNEXON
biosciences

STOP THE START

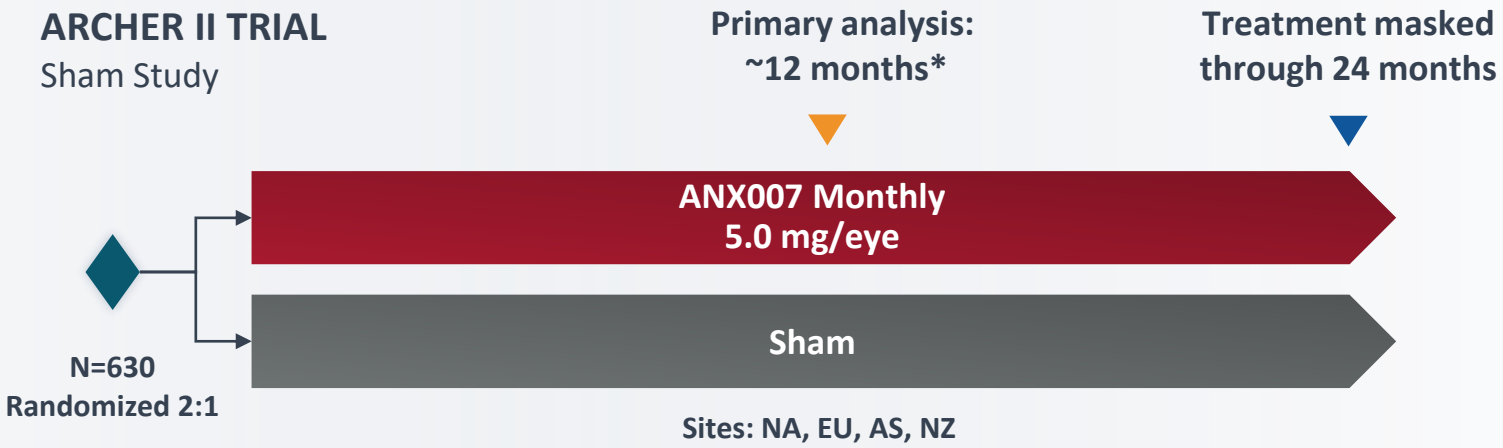
of classical
complement-driven
diseases

ANX007: What's Next?

ANX007 Global GA Phase 3 Program INITIATED

ARCHER II enrollment ongoing

PRIME designation from EMA



PRIMARY ENDPOINT

Persistent BCVA ≥15-Letter Loss through ~12 months*

*Primary analysis based on accumulation of BCVA ≥15-letter loss target events assessed between months 12-18 from initiation of dosing

SECONDARY ENDPOINTS

Safety, Low Luminance VA (LLVA), Ellipsoid zone (EZ)

ANNEXON biosciences

ANX007: A Novel Neuroprotective Agent Demonstrating Vision Protection Supported by Structure Protection Now in Phase 3

Blocking C1q for neuroprotection, prevented synapse loss and protected photoreceptors from elimination in animal models

ANX007, an anti-C1q Fab antibody administered IVT, **consistently protected against the loss of visual acuity** in the Phase 2 ARCHER study

Visual function benefit **supported by protection of retinal structures**, particularly those structures closely associated with visual function – **photoreceptors and foveal RPE**

ANX007 treatment was **generally well-tolerated;** no CNV increase; no reported cases of vasculitis

Regulatory-aligned Phase 3 program NOW ONGOING

ANNEXON biosciences

Thank you to the physicians, patients and care partners for their participation in the ARCHER and ARCHER II studies

ANNEXON biosciences

Questions